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The Journal of Pediatrics

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THE PHYSICAL GROWTH AND DEVELOPMENT OF CHILDREN WHO SURVIVED THE ATOMIC BOMBING OF HIROSHIMA OR NAGASAKI

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STANFORD, CALIF.

WITH THE TECHNICAL ASSISTANCE OF MILDRED L. GREULICH, B.SC., AND YOSHIO OKUMOTO, A.B.

IN THE summer of 1947, under the auspices of the National Research Council's Committee on Atomic Casualties and with the cooperation of the Public Health and Welfare Section of SCAP and of the Japanese National Institute of Health, two of us (W. W. G. and M. L. G.) made a preliminary survey of the physical growth and developmental status of children who had survived the atomic bombing of Hiroshima and Nagasaki. The data which we obtained included some physical measurements and x-ray films of the hand and wrist and of various other joint areas of children from the first six grades of elementary schools of those two cities. Comparable anthropometric and roentgenological observations were made also on children in Kure and Sasebo, who served as controls for those in Hiroshima and Nagasaki, respectively. The population of each control city was considered to be sufficiently similar to that of the city with which it was compared to justify the assumption that any significant difference in physical status between the children of a control and of an exposed city might reasonably be ascribed to the direct or indirect effects of the atomic bombing to which the latter had been subjected.

Dr. Frederick N. Snell, who, as a Navy Medical Officer, was then conducting some hematological and other studies for the Atomic Bomb Casualty Commission, aided greatly in our work in 1947, both by helping us to obtain access to children for study and in arranging for x-ray and other supplies needed in our project. We are greatly indebted to him for his generous assistance and to both him and Mrs. Snell for their cordial hospitality during our first visit to Hiroshima and Kure.

We returned to Japan, in the autumn of 1948, with the intention of repeating the examination of the children whom we had seen during the previous year and of making similar observations on additional cases. The Atomic Bomb Casualty Commission* preferred, however, that a re-examination of the Hiroshima and Kure children be postponed until its new labora-

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*Abbreviated "A.B.C.C." throughout the remainder of this paper.

tories were completed and its full program got under way in those two cities. Accordingly, we limited our activities in 1948 to Nagasaki, where we made observations on three different groups of children: those whom we had examined during the preceding year; additional exposed cases whom we had not previously studied; and a group of "internal controls" who, as explained below, had been substituted for the Sasebo children whom we had originally employed for that purpose.

TABLE I. NUMBER OF CHILDREN STUDIED

	ORIGINAL SERIES		ORIGINAL PLUS ADDED CASES	
YEAR	BOYS	GIRLS	BOYS	GIRLS
Hiroshima				
1947	66	79		
1949	53	66	169	161
1950	49	60	149	132
Kure				
1947	128	125		
1949	118	112	218	264
1950	90	71		
Nagasaki				
	EXPOSED		CONTROLS	
YEAR	BOYS	GIRLS	BOYS	GIRLS
1947	143	152		
1948	167	172	135	123
1950	149	154	126	117

The full program of the A.B.C.C. was begun in Hiroshima and in Kure early in 1949, at which time the children whom we had seen there in 1947 were re-examined by the staff and the x-ray and anthropometric data obtained from them were sent to us for study. The Nagasaki children whom we saw in the autumn of 1948 were not examined again until the autumn or winter of 1950-1951. The data obtained at the time of that examination were also made available to us. This report, accordingly, is based on the data collected during our preliminary survey in 1947 in Hiroshima, Kure, Nagasaki, and Sasebo; on those that we obtained on our second visit to Nagasaki, 1948; and on those derived from the re-examination by the A.B.C.C. staff of the Hiroshima and Kure children in 1949 and 1950 and of the Nagasaki children in late 1950 and early 1951. In Table I, the number of children on whom these observations were made is listed separately for each group and for each year covered by our study.

How the Children Were Selected.—Most of the children whom we studied in 1947 were selected by the local school and health officials of the four cities, with the assistance of Drs. M. Tamura and T. Shibayama, two physicians assigned to our project by the Japanese National Institute of Health, of Tokyo. In Hiroshima and Nagasaki, an attempt was made to limit the group to children on whom there was a definite history of epilation and radiation illness following the atomic bombing. It appears that this attempt was not entirely successful, for, in some cases, that history was denied when the parent or other surviving relative of the children was interrogated by a member of the A.B.C.C. staff some years later. It was confirmed, however, that all of the children in our "exposed" series had been in Hiroshima or in Nagasaki at the time of the atomic bombing.

Since the people principally responsible for the selection of the children had themselves been in those cities during 1945 and were well acquainted with the local population and the conditions obtaining there, it is assumed that the children whom they chose for our study were at least reasonably representative of those who had been exposed to the effects of the bombing. In Nagasaki, for example, the children were selected by Dr. Tamotsu Sano, who was then Professor of Pediatrics at the Nagasaki Medical School. In

1945, Professor Sano had made a survey of the children of school age who had been injured in the bombing and had issued some reports of his hematological and other studies of them in the latter part of that year. Most of the children in our original Nagasaki series were those on whom he had made previous observations.

In Kure and Sasebo, the children were selected so as to correspond in number and in age distribution to those in the Hiroshima and Nagasaki groups. As mentioned above, the Committee on Atomic Casualties decided, in 1948, to eliminate Sasebo as a control area and to use, instead, "internal controls"—children who were then in Nagasaki but who had not been there at the time of the bombing. We utilized this group from 1948 until the completion of our study.

FINDINGS

Height and Weight.—In order properly to evaluate our height and weight data, it seemed desirable not only to compare the height and weight of the Hiroshima and Nagasaki children with the height and weight of the children used as controls but also to determine how each group compared in these aspects of growth with children of the same sex and age in Japan as a whole during the early postwar period. The results of the latter comparison will be presented first.

In making this comparison, we utilized the height-weight-age tables based on data gathered by SCAP's Nutrition Survey of 1946-1947, under the direction of Colonel Paul Howe, of the Public Health and Welfare Section. This survey included the most extensive study of the height and weight of Japanese children that was made during the years immediately following the war, and its findings provide a very useful means of evaluating our own data. These P. H. & W. standards are reproduced in Table II. In using them we have, where necessary, modified the

TABLE II. STANDARD BODY HEIGHTS AND WEIGHTS FOR JAPANESE BY AGES
PUBLIC HEALTH AND WELFARE NUTRITION SURVEY, 1946-1947

AGE (YEARS)	STANDING HEIGHT (CENTIMETERS)				WEIGHT (KILOGRAMS)			
	MALE		FEMALE		MALE		FEMALE	
	MEAN	S.D.	MEAN	S.D.	MEAN	S.D.	MEAN	S.D.
1	75.9	6.0	74.7	5.8	9.2	2.0	8.8	1.5
2	84.5	5.8	83.3	5.5	11.5	1.8	11.0	1.6
3	91.3	5.0	90.2	5.2	13.3	2.0	12.8	1.7
4	97.5	5.2	96.3	5.1	15.0	2.1	14.3	1.8
5	103.1	5.5	102.2	5.6	16.3	2.1	15.8	2.0
6	108.1	5.5	107.2	5.5	17.7	2.2	17.2	2.2
7	111.0	5.8	110.8	5.8	19.4	2.4	18.6	2.3
8	116.0	5.9	115.0	5.5	21.2	2.5	20.4	2.3
9	121.0	6.0	119.0	5.8	23.3	3.5	22.4	3.2
10	125.0	6.0	124.0	6.0	25.2	4.0	24.7	3.7
11	129.0	6.5	129.0	6.0	27.6	4.2	27.5	4.2
12	134.0	7.0	136.0	7.5	30.5	5.5	31.5	5.1
13	140.0	8.0	141.0	7.3	34.5	5.5	35.9	5.8
14	148.0	8.0	145.0	6.8	39.2	6.1	40.4	5.9
15	153.0	8.0	148.0	6.0	45.3	7.0	43.6	5.9
16	157.0	7.5	149.0	5.7	49.2	7.0	45.9	5.7
17	159.0	7.2	149.0	5.6	51.6	6.2	47.4	5.8
18	161.0	6.2	149.0	5.6	53.2	6.0	48.4	5.8
19	161.0	6.2	149.0	5.5	54.1	5.6	48.8	5.7
20	161.0	6.0	150.0	5.0	54.5	5.5	48.7	5.6

average heights and weights so that they would correspond to the exact average age of the various groups of children in our series.

W. tables were based are summarized in Tables III and IV and in Figs. 1 and 2. In almost every instance, the average height and the average weight

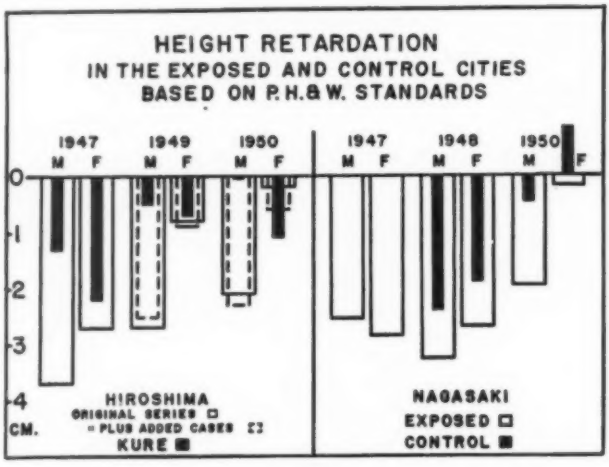


Fig. 1.

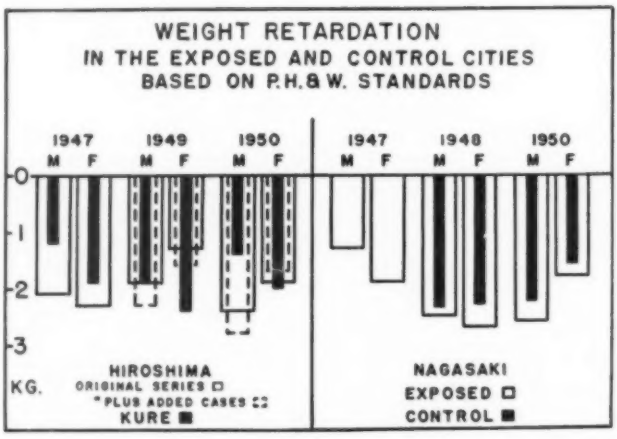


Fig. 2.

The Height and Weight of the Children in Our Series Compared With Those in the P. H. & W. Tables.—The observed differences between the average height and average weight of the children whom we studied and those of the children on whom the P. H. & of the children in our series were less than those assigned to children of the same sex and age in the P. H. & W. tables. Accordingly, our tables and figures have been constructed so as to show the magnitude of those deficits in height and weight. Some of them per-

tain only to those children who had been seen originally in 1947, while others are average values combining the heights or weights of that group separately for each sex, for each group, and for each year in which our observations were made. The corresponding deviations in average weight of the same children are shown similarly in Fig. 2.

TABLE III. STANDING HEIGHT
DEVIATION FROM P. H. & W. STANDARDS AT SUCCESSIVE EXAMINATIONS

		1947	1948	1949	1950
		CM.	CM.	CM.	CM.
Hiroshima					
Original series	Male	−3.7		−2.7	−2.1
	Female	−2.7		−0.8	−0.2
Original and added cases	Male			−2.5	−2.3
	Female			−0.9	−0.5
Kure					
Original series	Male	−1.3		−0.5	−0.02
	Female	−2.2		−0.7	−1.1
Original and added cases	Male			−0.2	
	Female			+1.0	
Nagasaki					
Exposed	Male	−2.5	−3.3		−2.0
	Female	−2.9	−2.7		−0.2
Nagasaki					
Control	Male		−2.4		−0.5
	Female		−1.9		+0.8

TABLE IV. WEIGHT
DEVIATION FROM P. H. & W. STANDARDS AT SUCCESSIVE EXAMINATIONS

		1947	1948	1949	1950
		KG.	KG.	KG.	KG.
Hiroshima					
Original series	Male	−2.1		−1.9	−2.4
	Female	−2.3		−1.3	−1.9
Original and added cases	Male			−2.3	−2.8
	Female			−1.6	−1.7
Kure					
Original series	Male	−1.2		−1.9	−1.4
	Female	−1.9		−2.4	−2.0
Original and added cases	Male			−1.8	
	Female			−2.0	
Nagasaki					
Exposed	Male	−1.3	−2.5		−2.6
	Female	−1.9	−2.7		−1.8
Nagasaki					
Control	Male		−2.4		−2.2
	Female		−2.3		−1.6

with those of other children from the same city who were added to the series in subsequent years.

In Fig. 1, the total average differences between the height of the children whom we studied and the height of those on whom the P. H. & W. standards were based are depicted

An examination of Fig. 1 discloses that, with only one exception (the girls of the Nagasaki control group in 1950, who exceeded the standards in stature), the children of both the exposed and control groups were all

somewhat below average in height, on the basis of the P. H. & W. standards. As is shown in Table V, the height deficits of the Hiroshima boys and those of the boys of the Nagasaki exposed groups were statistically significant at every year in which those children were examined. In most instances, however, the height deficits of the girls of the same groups were not significant.*

As is seen in Fig. 2, there was an even more consistent deficit in weight. Not only was the average weight of each of the groups of children studied —both the exposed and the controls— less than that of the P. H. & W. standards, but each of these differences was found to be significant.

During the period from 1947 to 1951, therefore, the children of both the exposed and control groups were somewhat shorter and lighter than the children of Japan as a whole were found to be in the early postwar years. Their deficits in height were significant in only fifteen of the twenty-six groups into which the children had been divided for study. These fifteen, however, included eleven of the sixteen exposed groups but only four of the ten groups of controls. Every group was significantly retarded in weight.*

TABLE V. THE SIGNIFICANCE OF THE DEFICITS IN AVERAGE HEIGHT OF THE DIFFERENT GROUPS OF CHILDREN STUDIED

	BOYS	GIRLS
Original Series		
Hiroshima	1947*	1947*
	1949*	1949
	1950*	1950
Kure	1947*	1947*
	1949	1949
	1950	1950
Nagasaki Exposed	1947*	1947*
	1948*	1948*
	1950*	1950
Nagasaki Controls	1948*	1948*
	1950	1950†
Original Series Plus Added Cases		
Hiroshima	1949*	1949
	1950*	1950

*Indicates that the average height of the group was significantly less than the corresponding value in the P. H. & W. standards.

†Exceeded the P. H. & W. standards in average height.

Every group of children had a significant *weight* deficit, on the basis of the same standards, at each year in which they were examined.

A Comparison of the Exposed With the Control Groups.—Some idea of the differences in average height and weight between the children who survived the atomic bombing of Hiroshima or Nagasaki and those who were used as their controls can be obtained from Figs. 1 and 2. These differences are shown in more detail, however, in Figs. 3 to 10, inclusive, in each of which the average height or weight of the boys or girls of an exposed city is compared

*For the sake of brevity, "significant" is substituted for "statistically significant" throughout the remainder of this paper.

*The statistical comparisons of the height and weight of different groups of children were made by the method suggested by Carroll Palmer[1] for treating similar data grouped by age but modified for the use of standard error instead of probable error. We have followed the convention of using $P = 0.05$ as expressing approximately the limit of significance.

with that of their controls of the same sex and chronological age.

The observed differences in height and in weight between the exposed and the control groups were evaluated statistically in order to determine whether

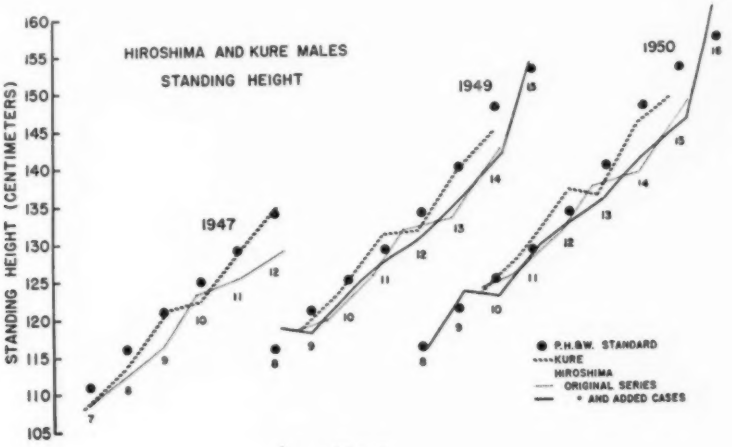


Fig. 3.

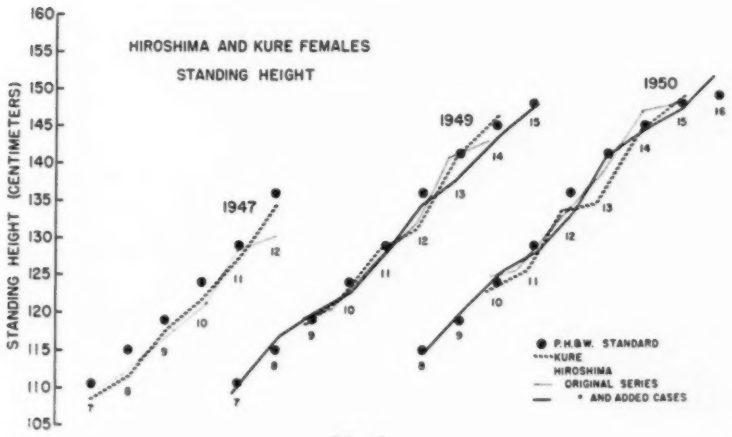


Fig. 4.

nificant. In 1949, the Hiroshima boys of the original series were still significantly shorter but not significantly lighter than the Kure boys. The two groups of girls did not differ significantly from each other in either height or not they were significant. In 1947 (Figs. 1, 2, and 3 to 6) the Hiroshima boys were significantly shorter and lighter than the Kure boys, but the corresponding differences between the girls in these two cities were not significant or weight. In 1950, the Hiroshima boys (original series) were still shorter than the Kure boys, but that difference was no longer significant, nor was their difference in weight. In that year, the girls showed no significant

difference in either height or weight.

There were some additional cases examined in Hiroshima and in Kure in 1949. Data on these same Hiroshima groups were available to us in 1950 also, but we did not have access to the 1950 data on the additional Kure cases. The data from both groups of added cases are listed in the tables, but only those from Hiroshima are included in the figures. An analysis of the differences in average height and weight between the combined (original plus additional cases) Hiroshima group and the corresponding combined Kure group in 1949 disclosed that both the boys and the girls from Hiroshima were significantly shorter than the Kure children, but that there was no significant difference in their weight.

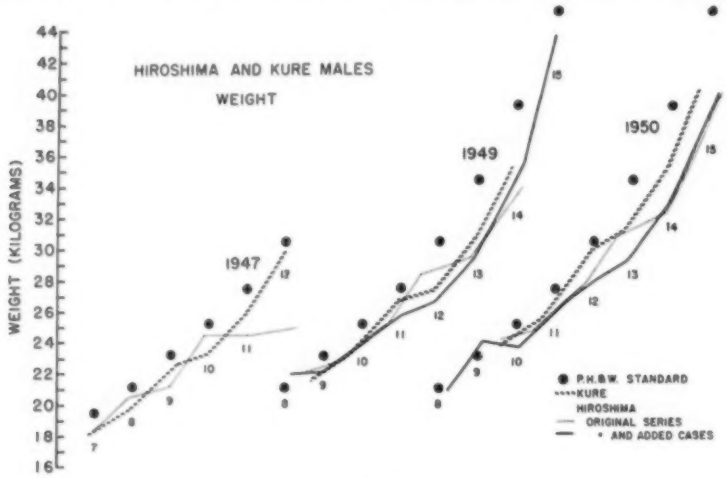


Fig. 5.

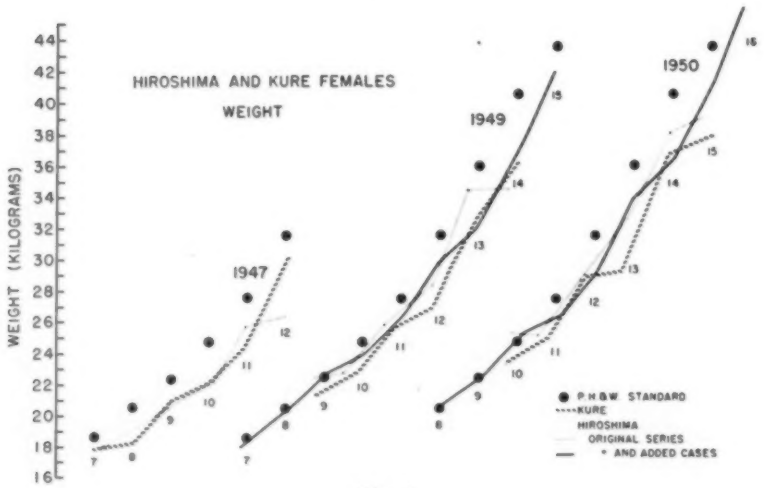


Fig. 6.

By rearranging the data of the original Kure cases into age groups corresponding to those of the large Hiroshima series, it was possible to compare the heights and weights of these two groups in 1949 and 1950. There was found to be no significant difference in height or in weight between the Hiroshima and Kure girls, in either year. In both years, however, the Hiroshima boys were significantly shorter than the Kure boys. They were also lighter than the latter in both years, but significantly so only in 1950.

A similar comparison of average height and weight of the Nagasaki children was possible only in 1948 and 1950, when observations were made on both the exposed and the internal control groups of that city. As is shown in Figs. 1, 2, and 7 to 10, the boys as well as the girls of the exposed group

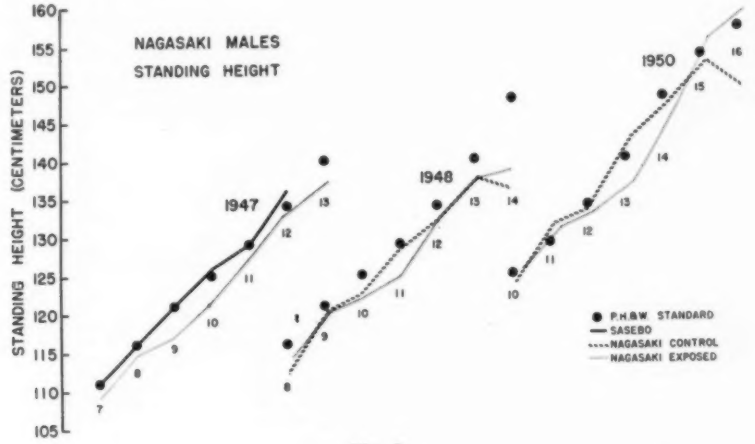


Fig. 7.

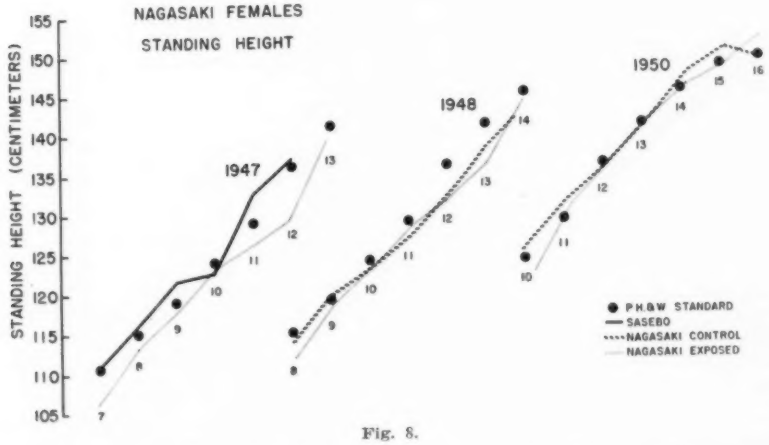


Fig. 8.

were somewhat shorter and lighter than the children of the same sex among the internal controls. None of these differences, however, was found to be significant. In neither 1948 nor 1950, therefore, was there any significant difference in height or weight between those Nagasaki children who survived the atomic bombing and those who were used as internal controls.

The accompanying outline (Table VI) represents an attempt to summarize our height and weight findings in a way that will facilitate their comparison.

In Figs. 7 to 10, the average heights and weights of the Sasebo children whom we used as controls in 1947 have also been included. Attention is directed to the fact that, even in 1947, the observed Sasebo values were much closer to those in the P. H. & W. tables

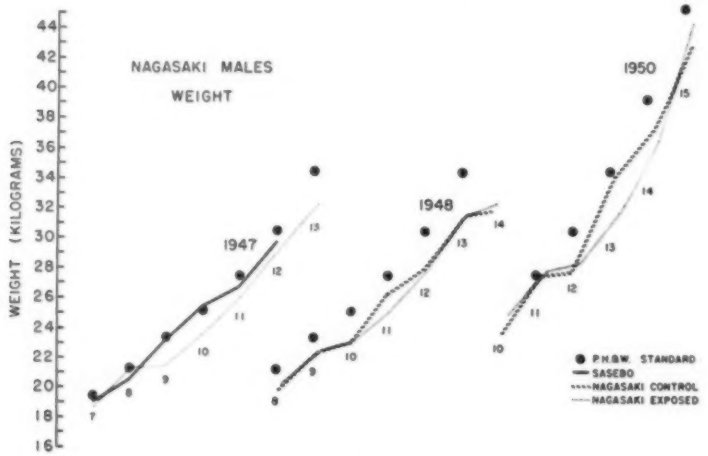


Fig. 9.

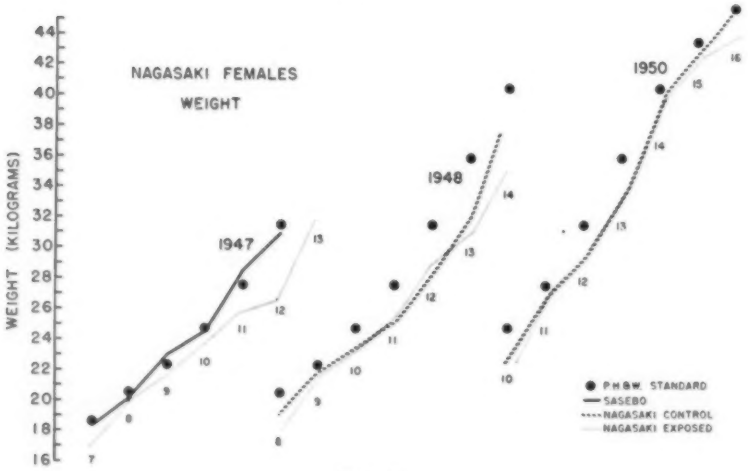


Fig. 10.

than were the average heights and weights of either the Kure group or those of the Nagasaki internal controls.

Skeletal Status.—In this report, skeletal status is described in terms of skeletal age based on the Greulich-Pyle standards of skeletal development of normal children.[2] Though the Greulich-Pyle standards, like the original standards of Todd,[3] which they were designed to replace, are based on the rate of skeletal development of well-circumstanced white children of the United States, they are quite useful, also, in comparing the skeletal status of groups of children of other races. The extent to which the rate or other features of skeletal development might be influenced by purely racial factors would, presumably, be shared by all children of that race. Any significant difference between the skeletal age of one group of children and that of a comparable group of the same race disclosed by the use of these standards indicates, therefore, a valid difference in the degree of their skeletal development.

The assessments of the x-ray films were made principally by two of us (C. C. and M. L. T.). During the early part of the study we were fortunate in having also in this work the collaboration of Drs. S. Idell Pyle and Nancy Bayley, to whom we are indebted for much helpful assistance.

It was found that the degree of skeletal development—the skeletal age—of the Japanese children whom we studied was not as advanced as that of

TABLE VI. A SUMMARY OF HEIGHT AND WEIGHT COMPARISONS OF THE EXPOSED AND THE CONTROL GROUPS

EXPOSED		CONTROLS
Hiroshima (Original Series)		*Compared with* *Kure (Original Series)*
Boys	1947	Significantly shorter and lighter than Kure boys
	1949	Significantly shorter than Kure boys but not significantly different in weight
	1950	No significant difference in either height or weight
Girls		No significant difference between exposed and controls in 1947, 1949, or 1950
Hiroshima (Original and Added Cases)		*Compared with* *Kure (Original and Added Cases)*
Boys	1949	Significantly shorter than Kure boys but no significant difference in weight
Girls	1949	Significantly shorter than Kure girls but no significant difference in weight
Hiroshima (Original and Added Cases)		*Compared with* *Kure (Original Cases Only)*
Boys	1949	Significantly shorter than Kure boys but no significant difference in weight
Girls	1949	No significant difference in height or weight
Boys	1950	Significantly shorter and lighter than Kure boys
Girls	1950	No significant difference in height or weight
Nagasaki (Exposed)		*Compared with* *Nagasaki (Controls)*
		No significant difference in height or weight between exposed and controls of either sex in 1948 or 1950

the children of the same sex and chronological age in the United States on whom our x-ray standards were based. The skeletal age of the Japanese children was, in general, somewhat less than their chronological age. In Tables VII and VIII and in Fig. 11, the skeletal status of the various groups

TABLE VII. A COMPARISON OF THE SKELETAL STATUS OF HIROSHIMA AND KURE CHILDREN

	RETARDATION OF SKELETAL DEVELOPMENT					
	(YEARS)			(PER CENT OF C. A.)		
	HIROSHIMA	KURE	DIFFERENCE	HIROSHIMA	KURE	DIFFERENCE
Hiroshima						
Original series						
1947						
Males	−2.49	−1.65	−0.84†	−27.7	−18.7	−9.0†
Females	−2.03	−1.86	−0.17	−22.3	−20.7	−1.6
Total	−2.26	−1.75	−0.51†	−25.0	−19.7	−5.3†
1949						
Males	−2.32	−1.75	−0.57†	−21.4	−16.7	−4.7*
Females	−1.99	−1.72	−0.27	−18.7	−16.1	−2.6
Total	−2.13	−1.74	−0.39†	−19.9	−16.4	−3.5†
1950						
Males	−2.06	−1.55	−0.51*	−18.1	−13.7	−4.4*
Females	−1.65	−1.54	−0.11	−14.3	−13.4	−0.9
Total	−1.84	−1.55	−0.29*	−16.1	−13.6	−2.5*
Original and added cases						
1949						
Males	−2.11	−1.75	−0.36*	−20.0	−16.7	−3.3*
Females	−1.78	−1.72	−0.06	−16.4	−16.1	−0.3
Total	−1.95	−1.74	−0.21*	−18.3	−16.4	−1.9
1950						
Males	−2.01	−1.55	−0.46†	−17.3	−13.7	−3.6*
Females	−1.61	−1.54	−0.07	−13.8	−13.4	−0.4
Total	−1.82	−1.55	−0.27*	−15.6	−13.6	−2.0

*Probability of 0.05 or less that such a difference would occur in random samples from the same population.

†Probability of 0.01 or less that such a difference would occur in random samples from the same population.

TABLE VIII. A COMPARISON OF SKELETAL STATUS IN EXPOSED AND CONTROL CHILDREN FROM NAGASAKI

	RETARDATION OF SKELETAL DEVELOPMENT					
	(YEARS)			(PER CENT OF C. A.)		
	EXPOSED	CONTROL	DIFFERENCE	EXPOSED	CONTROL	DIFFERENCE
Nagasaki						
1948						
Males	−2.32	−1.95	−0.37*	−21.8	−18.6	−3.2*
Females	−2.04	−1.83	−0.21	−18.9	−17.2	−1.7
Total	−2.18	−1.89	−0.29†	−20.3	−17.9	−2.4†
1950						
Males	−1.70	−1.36	−0.34*	−13.7	−10.8	−2.9†
Females	−1.59	−1.49	−0.10	−12.3	−11.7	−0.6
Total	−1.64	−1.42	−0.22*	−13.0	−11.3	−1.7*

*Probability of 0.05 or less that such a difference would occur in random samples from the same population.

†Probability of 0.01 or less that such a difference would occur in random samples from the same population.

of Japanese children is, accordingly, described in terms of the degree of their relative retardation in skeletal development. This is expressed as the difference between their age in years and their skeletal age at the time of each examination. If, for example, the average chronological age of a group was 9 years and the average skeletal age was only 7 years, it is recorded in the table as –2.0 years.

A comparison of the skeletal status of the Hiroshima children with that of the children in Kure is summarized in Table VII. It will be noted that, at every year in which observations were made, the Hiroshima boys were significantly retarded in their skeletal development as compared with the Kure boys. This was true of the original series as well as of the larger series of 1949 and 1950, which included both the children whom we had first seen in 1947 and the additional cases. The skeletal development of the Hiroshima girls also was more retarded than that of the Kure girls, but in no year was the difference found to be significant.

A similar situation was noted in Nagasaki, where in both 1948 and 1950 the boys and girls of the exposed series, i.e., those who had been in Nagasaki at the time of the atomic bombing, were more retarded in their skeletal development than were the children who were used as controls. Only in the case of the boys, however, was this difference found to be significant. These Nagasaki data are summarized in Table VIII.

The retardation in skeletal age of the boys in the exposed groups was sufficient to make the total average skeletal age of the boys and the girls in each exposed group significantly more retarded than that of the corresponding control groups.

The Hiroshima boys were not only more retarded in skeletal development than the Kure boys, but they were also more retarded skeletally than were the girls of their own city. This comparison is shown also in Table IX. It will be seen that in no year was the skeletal status of the Hiroshima boys

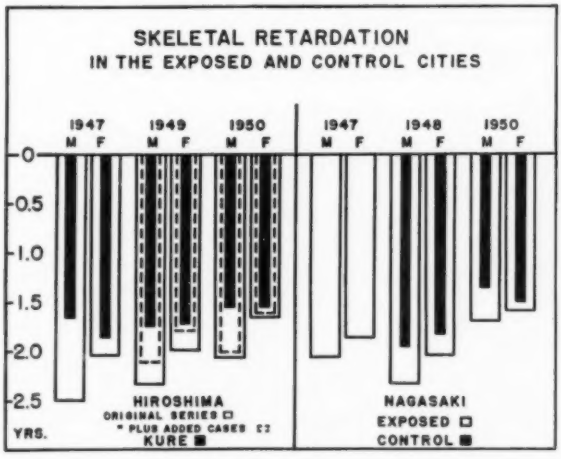


Fig. 11.

equal to or more advanced than that of the girls. The difference in skeletal status between the boys and the girls was significant in 1947 (original series) and also in 1949 and 1950 (original plus added cases).

The Kure boys were more advanced in their skeletal development than the Kure girls only in 1947, and the difference between them in that year was not significant. In 1949 and 1950 the Kure boys were only slightly more retarded skeletally than the girls, but, again, not significantly so.

In every group except the controls in 1950, the Nagasaki boys were found to be more retarded in skeletal age than the girls, at each year in which our observations were made. Only in the exposed group in 1948, however, was this difference significant (Table X).

In summary, the Hiroshima children were found to be more retarded in their skeletal development than the Kure children of the same sex in 1947, 1949, and 1950. The difference in skeletal age between them was, however, significant only in the case of the boys.

Similarly, in Nagasaki, in 1948 and 1950, the skeletal development of the

TABLE IX. THE SKELETAL STATUS OF MALES AS COMPARED WITH THAT OF FEMALES IN HIROSHIMA AND IN KURE

	RETARDATION OF SKELETAL DEVELOPMENT					
	(YEARS)			(PER CENT OF C. A.)		
	MALES	FEMALES	DIFFERENCE	MALES	FEMALES	DIFFERENCE
Hiroshima						
Original series						
1947	−2.49	−2.03	−0.46*	−27.7	−22.3	−5.4*
1949	−2.32	−1.99	−0.33	−21.4	−18.7	−2.7
1950	−2.06	−1.65	−0.41	−18.1	−14.3	−3.8
Original and added cases						
1949	−2.11	−1.78	−0.33†	−20.0	−16.4	−3.6†
1950	−2.01	−1.61	−0.40†	−17.3	−13.8	−3.5†
Kure						
1947	−1.65	−1.86	+0.21	−18.7	−20.7	+2.0
1949	−1.75	−1.72	−0.03	−16.7	−16.1	−0.6
1950	−1.55	−1.54	−0.01	−13.7	−13.4	−0.3

*Probability of 0.05 or less that such a difference would occur in random samples from the same population.

†Probability of 0.01 or less that such a difference would occur in random samples from the same population.

TABLE X. THE SKELETAL STATUS OF MALES AS COMPARED WITH THAT OF FEMALES IN NAGASAKI

	RETARDATION OF SKELETAL DEVELOPMENT					
	(YEARS)			(PER CENT OF C. A.)		
	MALES	FEMALES	DIFFERENCE	MALES	FEMALES	DIFFERENCE
Nagasaki						
Exposed						
1947	−2.06	−1.86	−0.20	−21.4	−19.2	−2.2
1948	−2.32	−2.04	−0.28*	−21.8	−18.9	−2.9*
1950	−1.70	−1.59	−0.11	−13.7	−12.3	−1.4
Controls						
1948	−1.95	−1.83	−0.12	−18.6	−17.2	−1.4
1950	−1.36	−1.49	+0.13	−10.8	−11.7	+0.9

*Probability of 0.05 or less that such a difference would occur in random samples from the same population.

boys and of the girls of the exposed group was more retarded than that of their controls. Again, it was the boys, and not the girls, who differed significantly from each other in this aspect of their development.

The skeletal development of the Hiroshima boys was less advanced than that of the girls of the same city, at every year in which our observations were made. The difference between them was significant in 1947 (original series) and in 1949 and 1950 (original plus added cases).

The Kure boys were more advanced skeletally than the Kure girls in 1947 but less advanced than they in 1949 and 1950. In no year was this difference found to be significant.

With the exception of the controls of 1950, the Nagasaki boys also were more retarded skeletally than the girls of their own group. This sexual difference in skeletal status was significant only among the controls in 1948.

The Improvement in the Physical Status of the Children During the Period of Observation.—One of the objectives of this study was to determine what improvement, if any, occurred in the growth and developmental status of the Hiroshima and Nagasaki children during the period of our observation, and how that progress or lack of it compared with that of the children in Kure and Nagasaki who were used as their controls. This section presents the results of a comparison of their progress as determined by the extent to which, at successive examinations, each group of children deviated in height, weight, and skeletal development from the standards used in the study.

There is a practical difficulty in evaluating the deviation of the various groups of children in stature or in weight from the P. H. & W. standards in successive years. Since children ordinarily increase in height and in weight as they grow older, a deviation of, let us say, 4 centimeters or 3 kilograms from a height-weight-age standard at 7 years is somewhat more serious than the same deviation in children who are several years older. In an attempt to achieve a greater degree of comparability of our data, we have expressed each deviation from the P. H. & W. standards as the percentage which it represents of the average height or weight of the group of children in which it was observed. A comparison of the percentage deviations in height and weight of the children of the exposed and control groups at successive examinations provides a useful measure of their progress in physical growth during the period from 1947 to 1950.

These percentage deviations in height and in weight are listed in Tables XI and XII and are shown graphically in Figs. 12 and 13. It will be noted that in every group the deficit in average height of both the boys and the girls was smaller on the basis of the P. H. & W. standards in 1950 than it had been in 1947. Indeed, in two instances, the average stature exceeded the standard value.

The boys of the exposed group in Nagasaki were remarkable, in that their retardation in height was even greater in 1948 than it had been in 1947. Since, however, no data were gathered in Hiroshima or Kure in 1948, we cannot be sure that the children of those cities also were not simi-

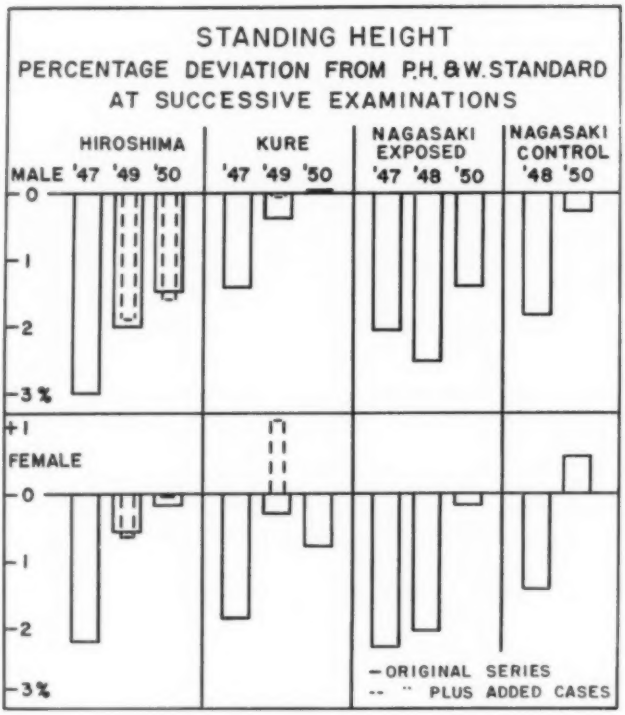


Fig. 12.

TABLE XI. STANDING HEIGHT
PERCENTAGE DEVIATION FROM P. H. & W. STANDARDS AT SUCCESSIVE EXAMINATIONS

		1947	1948	1949	1950
Hiroshima					
Original series	Male	-3.01		-2.03	-1.49
	Female	-2.20		-0.58	-0.17
Original and added cases	Male			-1.87	-1.60
	Female			-0.62	-0.03
Kure					
Original series	Male	-1.43		-0.37	+0.03
	Female	-1.87		-0.28	-0.79
Original and added cases	Male			-0.05	
	Female			+1.11	
Nagasaki					
Exposed	Male	-2.05	-2.51		-1.40
	Female	-2.27	-2.02		-0.16
Nagasaki					
Control	Male		-1.83		-0.29
	Female		-1.41		+0.56

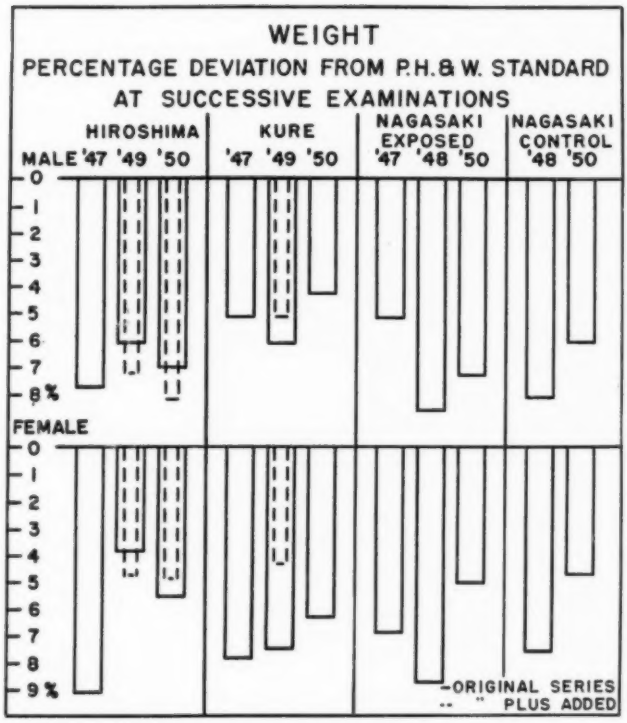


Fig. 13.

TABLE XII. WEIGHT
PERCENTAGE DEVIATION FROM P. H. & W. STANDARDS AT SUCCESSIVE EXAMINATIONS

		1947	1948	1949	1950
Hiroshima					
Original series	Male	−7.74		−6.10	−7.02
	Female	−9.13		−3.88	−5.56
Original and added cases	Male			−7.26	−8.19
	Female			−4.72	−4.85
Kure					
Original series	Male	−5.14		−6.13	−4.22
	Female	−7.84		−7.48	−6.31
Original and added cases	Male			−5.20	
	Female			−4.36	
Nagasaki					
Exposed	Male	−5.16	−8.56		−7.36
	Female	−6.82	−8.73		−5.05
Nagasaki					
Control	Male		−8.12		−6.04
	Female		−7.60		−4.70

larly retarded at that time.* In any case, by 1950, the deficit in stature of the boys of the exposed groups in Nagasaki, though less than it had been in 1947 or 1948, was still greater than that of the girls of the same group and greater, also, than that of either the boys or the girls of the controls.

Weight is a much more variable measure than height, because, unlike the latter, it is reversible and more readily influenced by a variety of factors, favorable and unfavorable. The general trend in weight over the period from 1947 to 1950 was, however, similar to that observed in the height of the same children.

which the deficit in weight of both the boys and the girls was greater in 1950 than it had been in 1949. The weight deficit of the boys of the combined Hiroshima group in 1950 was also larger than that of the boys of the original Hiroshima series in 1947.

On the basis of their percentage deviation in weight from the P. H. & W. standards, the boys and the girls of the exposed and the control groups in Nakasaki were more retarded in weight in 1948 than the children of the same sex in the exposed group had been in 1947. By 1950, the girls of both groups had more than made up their weight deficit and deviated less

TABLE XIII. SKELETAL AGE
PERCENTAGE DEVIATION FROM GREULICH-PYLE STANDARDS AT SUCCESSIVE EXAMINATIONS

		1947	1948	1949	1950
Hiroshima					
Original series	Male	−27.7		−21.4	−18.1
	Female	−22.3		−18.7	−14.3
Original and added cases	Male			−20.0	−17.3
	Female			−16.4	−13.8
Kure	Male	−18.7		−16.7	−13.7
	Female	−20.7		−16.1	−13.4
Nagasaki					
Exposed	Male	−21.4	−21.8		−13.7
	Female	−19.2	−18.9		−12.3
Control	Male		−18.6		−10.8
	Female		−17.2		−11.7

The children of the original Hiroshima and Kure series of each sex were somewhat less retarded in weight in 1950 than they had been in 1947. A different relationship is seen in the larger group of Hiroshima children (the original plus the added cases), in

from the standards than had the Nagasaki children in 1947. The boys of the exposed and the control groups in 1950, though less retarded than they had been in 1948, were still relatively more underweight than were the boys of the exposed group in 1947.

Table XIII and Fig. 14 show the percentage deviations in the skeletal age of the various groups of children as determined by the use of the Greulich-Pyle x-ray standards. In each case the value tabulated or graphed

*Without being aware of our findings, Colonel Howe, in a personal communication to the senior author, wrote that there was "something peculiar" about the growth of Japanese children in 1948, in that their preadolescent spurt of growth was not as pronounced as usual, according to the data collected *in various parts of Japan* by his coworkers in that year. Neither he nor they knew of any special circumstances affecting the rate of growth to which this peculiarity could be attributed.

is the observed average retardation in skeletal age expressed as the percentage which that retardation represents of the average chronological age of the children at the time their x-ray films were made. The usefulness of the degree of differentiation of the skeleton for determining the general developmental status of the child is illustrated by the somewhat greater consistency of the trends as shown in this figure and table as compared with the corresponding percentage deviations in height and weight of the same children.

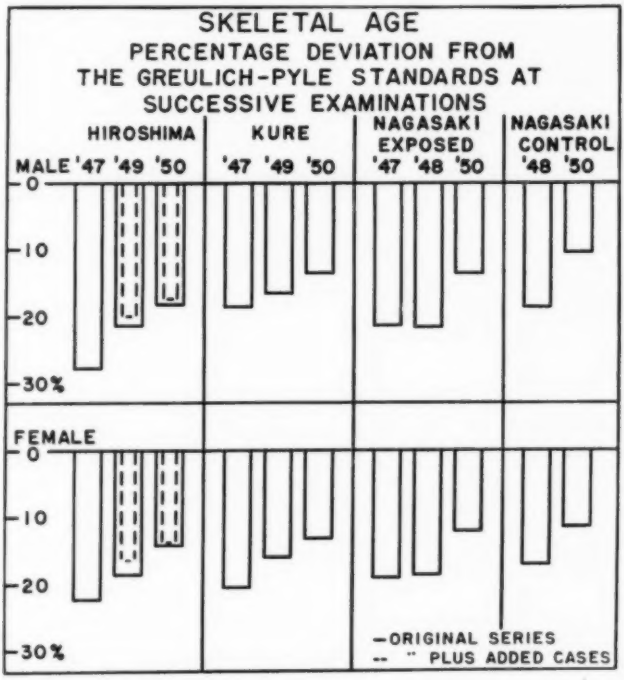


Fig. 14.

The children of each sex and of each group of exposed as well as controls showed a definite improvement in their skeletal status in 1950 as compared with 1947 or 1948. The degree of skeletal retardation was, in most instances, somewhat greater in the boys than in the girls. Both the Hiroshima and the Nagasaki exposed groups were more retarded skeletally than were their controls, at every examination. This remained true even though the children of the exposed groups improved relatively more in their skeletal status than did the controls between 1947 and 1950.

In summary, when the observed changes in average standing height, weight, and skeletal age are expressed as percentage deviations from appropriate standards, the following facts are disclosed:

Over the period from 1947 to 1950, a definite improvement occurred in the average height, weight, and skeletal status of all but two of the groups of children studied. The exceptions were the boys of the exposed groups in

Hiroshima (combined series) and in Nagasaki, whose deficits in weight in 1950 were relatively greater than they had been three years earlier.

In 1950, the Kure boys were farther advanced in height, weight, and in skeletal status than the Hiroshima boys of either the original or the combined series. The Kure girls, however, were more retarded than the Hiroshima girls of both series in height and in weight, but slightly more advanced than they in skeletal status. The boys and the girls of the Nagasaki controls were superior to the children of the same sex in the Nagasaki exposed group in all three of these measures.

Thus, it is seen that, with the exception of the Kure girls, all the various control groups in 1950 maintained in only a slightly reduced degree the superiority in height, weight, and in skeletal development which they possessed in 1947. Stating it differently, those children who survived the atomic bombing of Hiroshima or of Nagasaki, despite their slightly more rapid progress in growth and development during the period of our observations, still lagged somewhat behind the children who were used as their controls, in 1950. As mentioned previously, the Kure girls did not conform to this pattern except in their skeletal status, since they were on the average shorter and lighter in 1950 than the Hiroshima girls with whom they were compared.

As is shown in Figs. 12 and 13, the Kure girls of the original series were much more retarded in height and weight than were the girls of the larger Kure series (the original plus the added cases) in 1949 which, unfortunately, was the only year in which the data on this combined group were made available to us for study. This suggests that our original series was not adequately representative of the girls of Kure—at least, not of that group in 1949 and subsequently—in that it included too many who were undersized and underweight as a result of illness or malnutrition. It is regrettable that we did not have access to subsequent data on the large Kure series, for they would have enabled us to make a rather more satisfactory comparison of the physical status of the Kure and Hiroshima girls.

Some Additional Observations.—Thus far, we have discussed principally the data based on total average heights, weights, or skeletal ages of the various groups of exposed and control children. Some valuable supplementary information can be derived from a consideration of the curves of height and weight of individual age groups of children during the period covered in our study. These can be followed in Figs. 3 to 10, which relate the average height or weight of each group of boys or girls to their chronological age at the time of their examinations in 1947, 1948 or 1949, and 1950 and to the corresponding average height or weight in the P. H. & W. standards.

The children ranged in age from 7 to 12 or 13 years in 1947, when they were first examined. In the figures, the chronological ages are printed below the large black dots, each of which indicates the P. H. & W. standard height or weight appropriate to that age. In each figure, the average heights or weights of an exposed and a control group are plotted so that the dimensions at various chronological ages can be compared with each other and with the corresponding P. H. & W. value at successive examinations. The reader's

attention is invited to the following examples which illustrate the kinds of information that can be derived from these figures.

In Fig. 3, it will be noted that the average height of the 9-year-old Kure boys in 1947 closely approximated that of the boys of the same age on whom the P. H. & W. standards were based. In 1949, when the same group of boys were 11 years old, their height exceeded slightly the corresponding P. H. & W. value, and that superiority in height had further increased in 1950 when they were 12 years of age. On the other hand, the Kure boys who were 10 years old in 1947 were below the standards in height at that time and tended to remain so throughout the period of observation. The progress in height and weight of any age group can be followed similarly in these two figures.

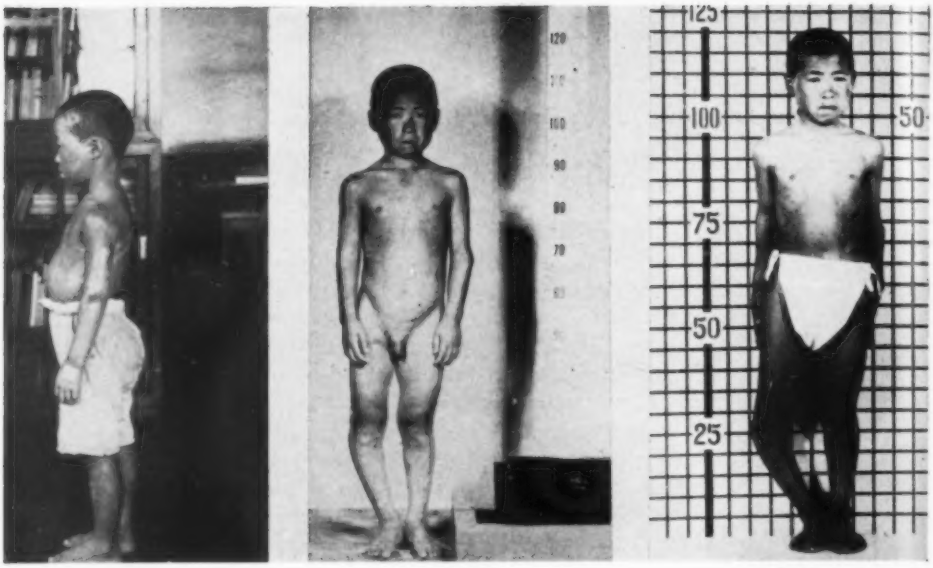
The figures show also the greater variability of weight as compared with height of the individual age groups of children studied; the general improvement in the height and weight of the children during the period of observation; the similarities and dissimilarities between the growth curves of the children of the original and of the combined Hiroshima series; and the somewhat greater retardation of the boys as compared with the girls of the same group in height and weight.

The different trends in height of the two Kure age groups just considered illustrate how the average heights or average weights of large groups of children can easily obscure interesting and, perhaps, significant differences in growth rate of the individual age or other subgroups of which they are composed.

Because they add but little to the data already presented, we feel that no useful purpose would be served by a detailed discussion of the other physical measurements that were made of the same children on whom this report is based. In general, they tend to conform to the trends disclosed by the data that have already been analyzed.

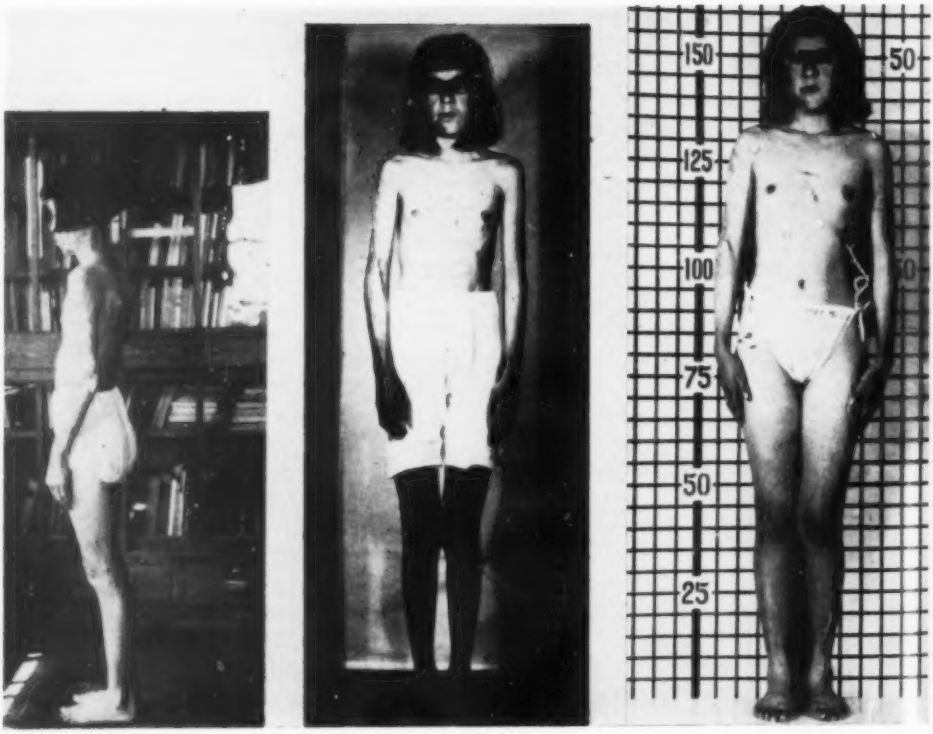
A very useful supplement to the anthropometric and x-ray data in revealing the progress of these children in physical growth and development during the period of observation is afforded by a comparison of their photographs taken at successive examinations. Serial photographs of a number of children of the Nagasaki exposed group are shown in Figs. 15 to 20. In addition to having a history of epilation and radiation sickness, these children were among those who survived the most severe thermal burns or other traumatic injuries incurred at the time of the atomic bombing of that city. Their improvement during the period from the summer of 1947 to the end of 1950 is believed to be reasonably typical of the more severely injured Nagasaki children.

As can be seen in the accompanying photographs, some of the wounds of the children had not completely healed by 1950, more than five years after the injury which produced them. The possibility of malignancies eventually developing at these sites cannot be ignored. It is well known that malignancies occasionally develop at the site of old thermal burns and that x-ray and other radiation can, under certain conditions, also produce them. Some of the children in Hiroshima and Nagasaki received both types of injuries almost simultaneously. One wonders if the tissues will respond in a quantitatively or qualitatively different way to such a double insult as compared with their response to either type of



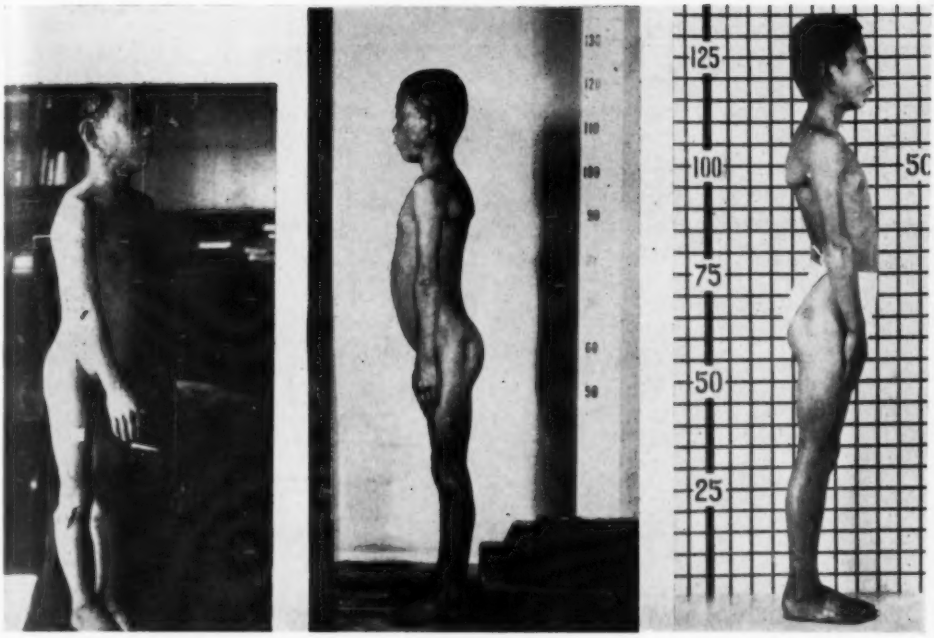
1947 1948 1951

Fig. 15.



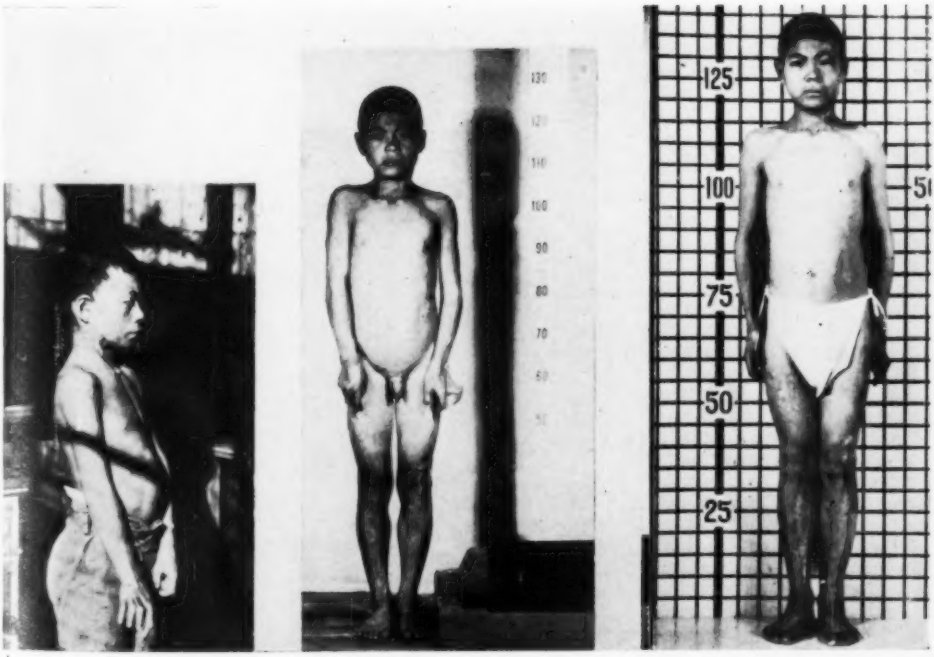
1947 1948 1951

Fig. 16.



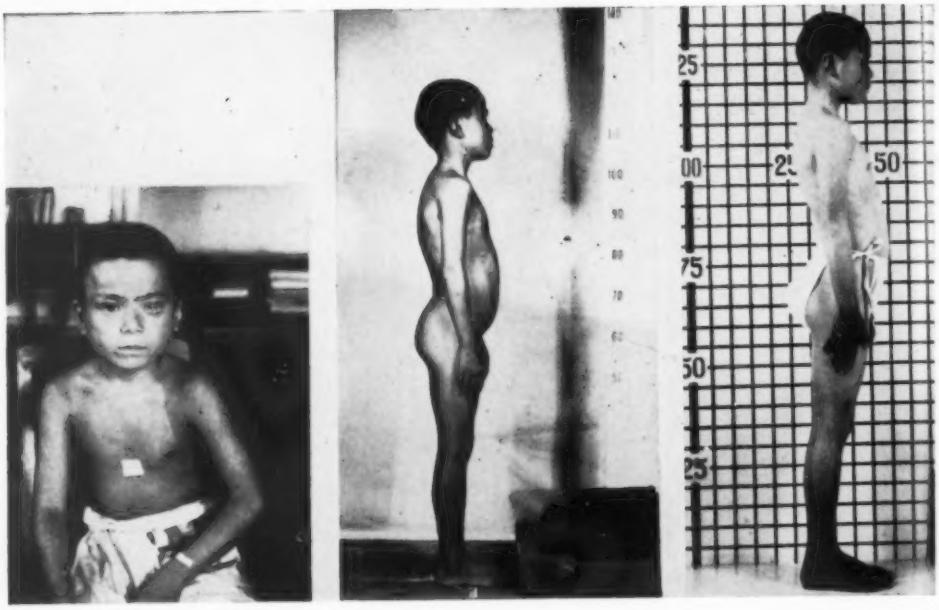
1947 1948 1950

Fig. 17.



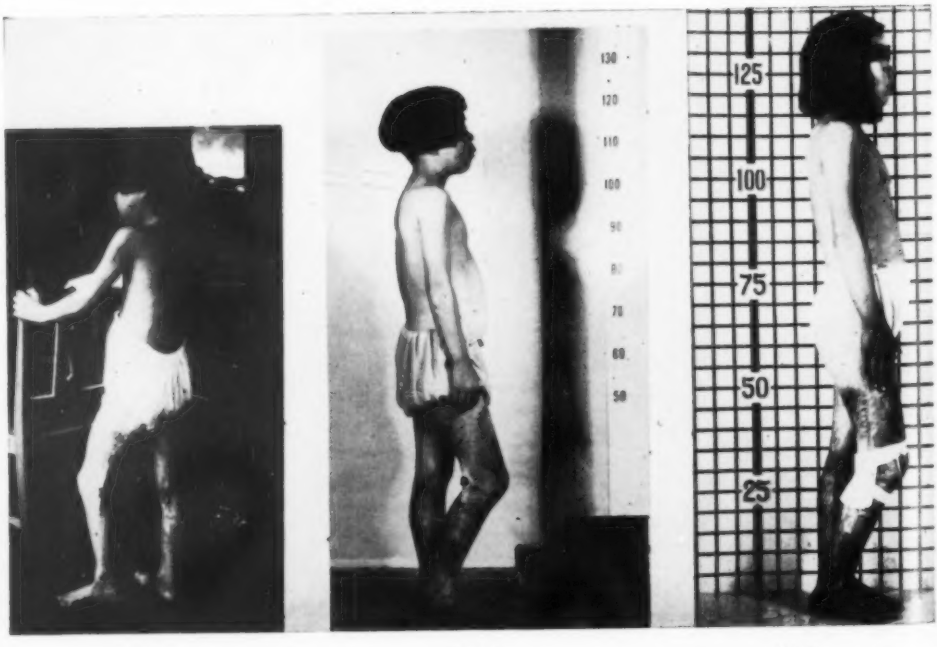
1947 1948 1951

Fig. 18.



1947 1948 1951

Fig. 19.



1947 1948 1950

Fig. 20.

injury alone. In any case, these scars and the unhealed lesions deserve the close attention that they will certainly receive from the clinicians who are following the progress of the Hiroshima and Nagasaki children.

CONCLUSIONS

Our findings indicate that the physical growth and development of the children who survived the atomic bombing of Hiroshima or Nagasaki were adversely affected by that experience and that some of the resulting retardation in their height, weight, and skeletal development was still evident at the end of 1950, five and one-half years after the bombing.

It should be emphasized that these deficits still persisted despite the marked improvement in the food supply and in the general economic conditions that had taken place during the intervening years. It should be remembered, also, that, as late as the end of 1950 and the beginning of 1951, the Hiroshima children and those of the Nagasaki exposed group were still somewhat below the average heights and weights that the children of the same sex and age in Japan as a whole had achieved by 1946 and 1947 and which, presumably, the latter had surpassed in the interim.

In general, the boys tended to be more retarded than the girls of the same group. This is consistent with our observations in Guam[4] and elsewhere that boys appear to withstand less successfully than girls the rigors of an unfavorable environment and to require a longer period than they to recover from its untoward effects.

The adverse effects on the growth and development of the Hiroshima and Nagasaki children disclosed in this study probably derived from a variety of causes. These include the harmful action of the thermal and other types of radiation from the atomic bomb itself; the other physical injuries incurred at the time of the bombing; the severe psychological traumas which resulted from witnessing a horrible form of violent death that, in many instances, claimed parents, siblings, neighbors, and friends; and the subsequent severe disruption of the economy with the extreme poverty, the widespread malnutrition, and the other evils that follow in the wake of such an overwhelming disaster. It is futile to attempt to dissociate these factors or to allocate to each its proper share of responsibility for the effects observed. They are, to a large extent, inseparable and inevitable consequences of the kind of cataclysm which produced them.

This study was possible only because of the cooperation and collaboration which we received from many persons both here and in Japan. We can acknowledge here our indebtedness to only some of those who contributed most to the success of the project. They are: Dr. Austin Brues, who first transmitted our proposal for the study to the National Research Council's Committee on Atomic Casualties; Dr. Herman Wigodsky, Professional Associate of the Committee, whose unfailing helpfulness placed us permanently in his debt; Lt. Col. Carl F. Tessmer and his successor as Director of the Atomic Bomb Casualty Commission in Japan, Dr. Grant Taylor, both of whom generously made available to us the services of their staff and the facilities of their laboratories; Dr. Atsuyoshi Takao, to whom we are indebted for most of the anthropometric data obtained after 1948; and Drs. Arthur Tucker, Wataru Sutow, M. Suzuki, and Arthur Pryde who in various ways aided greatly in facilitating our study.

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LEAD POISONING: ROENTGENOGRAMS OF THE CHEST AS AN AID IN DIAGNOSIS

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PARK, in 1930, in discussing a paper on congenital syphilis of bone by McLean[1] was presumably the first to call attention to dense bands at the ends of long bones as evidence of lead poisoning. In the same year Vogt[2] described and illustrated dense zones at the ends of all of the actively growing bones. In this paper he included a posteroanterior film of the chest in which the anterior rib ends were unusually dense near their costochondral junctions. These densities were more marked in the middle six ribs. In 1931, Caffey[4] demonstrated some rib ends on a lateral film of the chest of a dog that had succumbed to lead poisoning.

In spite of the above observations, attention is rarely directed to bones other than those of the extremities in the roentgenographic search for evidence of lead poisoning in infants and children. In view of recent experiences with two infants with lead poisoning, it seems justifiable to re-emphasize the importance of the changes which occur in the anterior ends of ribs.

For the infant whose history and clinical findings are suggestive of lead poisoning, the various diagnostic aids are utilized immediately to establish the diagnosis so that therapy may be instituted as soon as possible. In such instances, a request for roentgenographic examination of the long bones is customary. The possibility of lead poisoning is not always considered in the case of infants and young children who are admitted to the hospital with vague complaints referable to the abdomen and/or the central nervous system. Frequently, there is no history of chewing of paint from furniture, woodwork, or toys, or of other possible sources of ingestion or inhalation of lead. In these patients, roentgenograms of the long bones are not usually obtained, but films of the chest are frequently taken.

Recently, two infants were observed in whom the diagnosis of lead poisoning was suspected just prior to death. Radiographs of the anterior ends of several ribs obtained at autopsy revealed definite zones of increased density suggestive of heavy metal poisoning (Fig. 3) and staining of the ends of the ribs by the "sulfide" technique resulted in lead sulfide deposits at the zones of increased density.

CASE REPORTS

CASE 1.—C. L., a 2-year-old Negro girl, was admitted to the hospital with a history of intermittent fever, lethargy, irritability, and vomiting, of two days' duration. Physical examination revealed an acutely ill, stuporous child who was aroused only with difficulty, but who would respond enough to ask for water. The temperature was 102° F., and there

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was moderate dehydration. The mucous membranes were pale, the pupillary reflexes were normal, and nuchal rigidity was present. No abnormalities were noted in the chest or abdomen. The initial diagnostic impression was tuberculous meningitis. The roentgenogram of the chest taken on admission to the hospital did not reveal any pathologic lesion of the heart or lungs. The spinal fluid was clear and contained only two cells per cubic millimeter. The protein content was elevated.

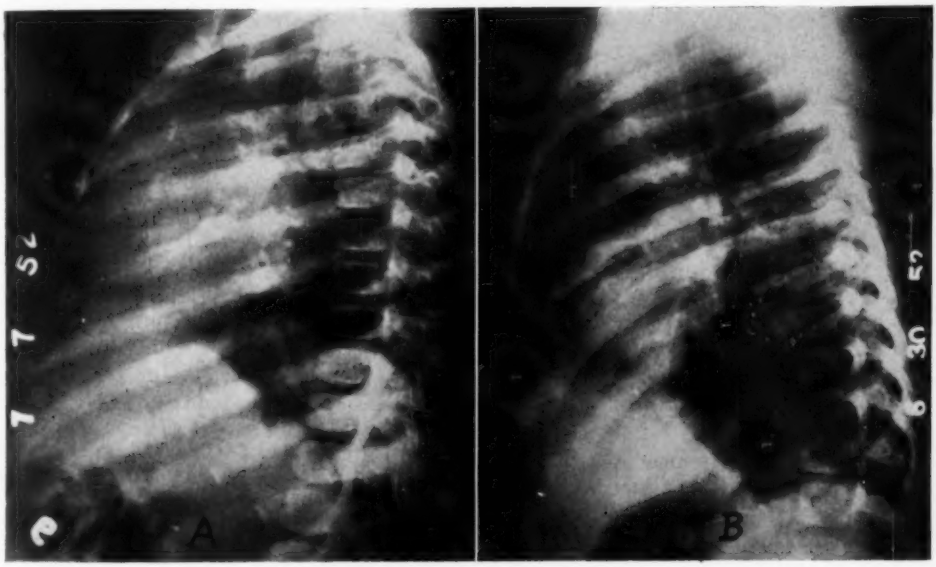

Fig. 1.—*A*, Case 1. Lateral roentgenogram of the chest of an infant with lead poisoning. Note dense rib ends. *B*, Lateral roentgenogram of the chest of a healthy infant of the same age (same degree of obliquity) with no evidence of zones of density at the ends of the ribs.

Vomiting continued intermittently so that hydration by the administration of intravenous fluids was required. The general condition did not change appreciably until twenty-four hours following admission when she began to convulse. At this time, a second lumbar puncture was performed. The spinal fluid pressure was low and the protein was 175 mg. per cent. Following this procedure, the child became cyanotic and temporarily ceased to breathe. Artificial respiration and oxygen were administered with some slight improvement in the patient's condition. In view of the possibility of herniation of the cerebellar tonsils, another lumbar puncture was performed to replace the fluid removed with physiologic saline solution. This procedure had no beneficial effect and bilateral trephine openings were made in the skull. On opening the dura there was immediate herniation of cortical tissue. Only 2 c.c. of fluid was obtained from each lateral ventricle and repeated attempts failed to obtain additional fluid. The child never resumed normal respiratory movements and died three hours following the operative procedure. Post-mortem examination revealed no gross pathologic findings except moderate edema of the brain and flattening of the convolutions.

CASE 2.*—P. M., a 21-month-old Negro female child, was admitted to

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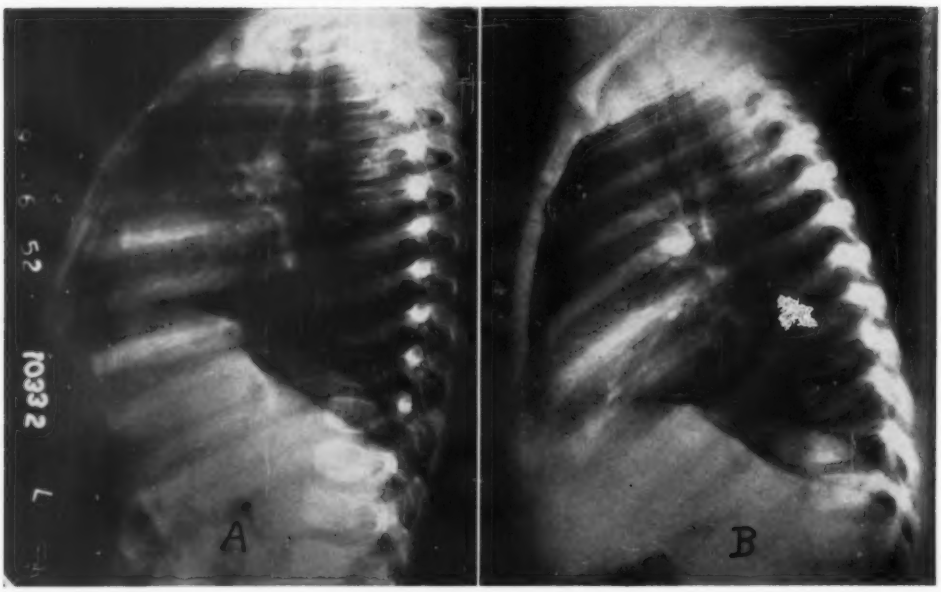

Fig. 2.—*A*, Case 2. Lateral roentgenogram of the chest of an infant with lead poisoning showing sharply defined rib ends and zones of oval density. *B*, Lateral roentgenogram of the chest of a healthy infant of the same age for comparison.

Fig. 3.—*A*, Radiograph of a normal rib end from a child 2 years of age. *B*, Rib ends from Case 2. Note the wide zone of increased density at the ends of these ribs.

the hospital with a history of vomiting two or three times daily for a period of nearly five weeks. Dietary modifications had given no relief. For three days prior to admission the child was constipated. The mother reported that the child had seemed unusually nervous during the entire five-week period. The initial diagnostic impression was intestinal obstruction.

Physical examination revealed a poorly nourished child who was obviously dehydrated. There was evidence of generalized irritability but otherwise the examination was not remarkable.

A roentgenogram of the chest taken on the day following admission did not reveal any abnormalities of the heart and lungs. Films of the abdomen made in the supine and erect positions did not show any roentgenologic evidence of intestinal obstruction.

Late on the afternoon of the third day in the hospital, the child had a convulsion. A lumbar puncture was performed. The spinal fluid was clear; the pressure was within normal limits and the protein was 121 mg. per cent. Anemia was present, but there was no basophilic stippling. Roentgenograms of the long bones revealed broad zones of increased density at the metaphyses.

Despite sedation and bitemporal decompression, the convulsions continued and the child expired on the fourth hospital day.

Post-mortem radiographs of rib ends from this patient are shown in Fig. 3.

DISCUSSION

Each of these patients had roentgenograms of the chest shortly after admission (Figs. 1 and 2). A review of these films showed zones of increased density at the anterior ends of the ribs which, had they been noted originally, should have aroused suspicion of possible heavy metal poisoning. Since the clinical course in these two patients was rapidly downhill, it is doubtful that an early diagnosis of lead poisoning would have changed the outcome. However, had lead poisoning been suspected, the form of therapy might have been altered.

The demonstration of dense zones at the ends of the ribs in these two infants stimulated a review of ten additional cases of lead poisoning. In each of these, dense zones at the anterior ends of the ribs were demonstrated in either the lateral or posteroanterior roentgenogram of the chest. (Figs. 4 and 5 illustrate two of these cases.) There was a sharp line of demarcation between the bone and cartilage at the costochondral junction, with a dense zone at the anterior costal end. A comparison with roentgenograms of the chest of healthy infants and children of the same age group showed that the anterior ends of the ribs were less well defined, with absence of the dense zones. It should be recalled, however, that the metaphyseal ends of long bones may show a zone of increased density which may be the result of normal active bone growth. Large doses of vitamin D or healing rickets often produce dense zones similar to those observed in mild cases of heavy metal poisoning.

It has been well established that when clinical manifestations and history indicate the possibility of lead poisoning the roentgenograms of the long bones are of great value in substantiating the diagnosis. Changes resulting from lead poisoning, however, may be observed not only in the long bones of the body but also in any of the other actively growing

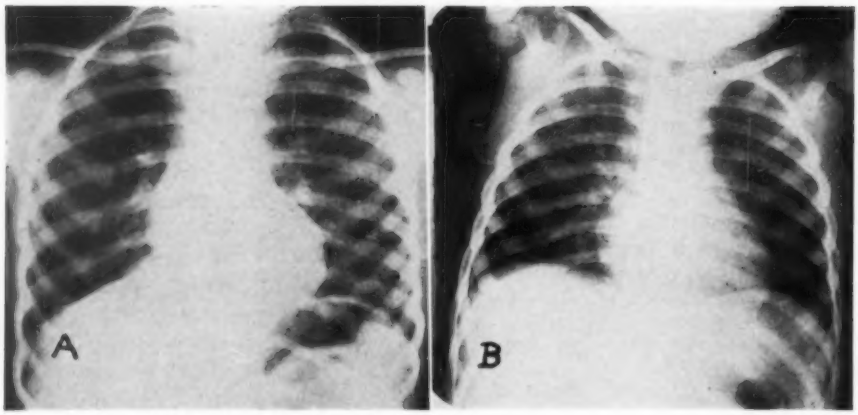

Fig. 4.—*A*, Roentgenogram of the chest of an infant with lead poisoning demonstrating dense anterior ends of ribs on the right side. *B*, Roentgenogram of the chest of a healthy infant of the same age for comparison.

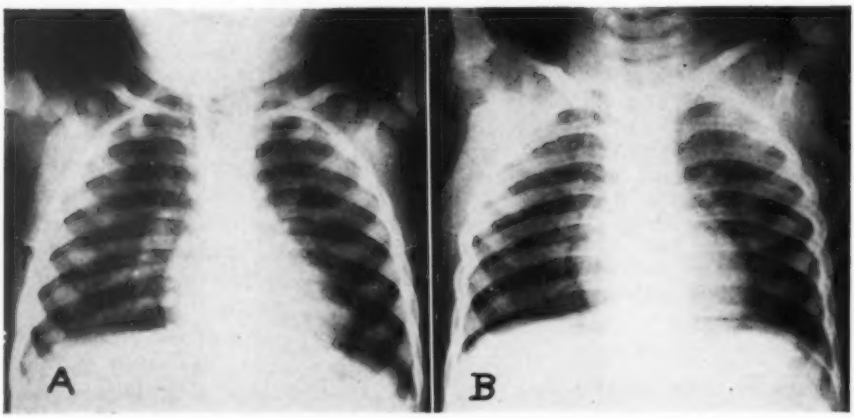

Fig. 5.—*A*, Anteroposterior roentgenogram of the chest of an infant with lead poisoning. The anterior ends of the ribs on the right side show increased density. Also note the dense zones at the proximal metaphyseal ends of humeri and at the inferior angles of scapulae. *B*, Roentgenogram of the chest of a healthy infant of the same age for comparison.

bones, i.e., rib ends, crests of ilia, and margins of scapulae. In the atypical or unsuspected cases of lead poisoning, roentgenograms of the chest may thus provide the first diagnostic clue.

SUMMARY

1. Two fatal cases of lead poisoning in children are presented in which more careful analysis of the roentgenograms of the chest might have resulted in an earlier diagnosis.

2. A review of ten additional cases of lead poisoning has also revealed dense zones at the anterior ends of the ribs on roentgenograms of the chest.

3. These observations emphasize the importance of careful scrutiny of the anterior ends of ribs on all roentgenograms of the chests of infants and children.

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CHARCOT-MARIE-TOOTH DISEASE

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IN RECENT literature, there has been little reference made to Charcot-Marie-Tooth disease. It has been confused by some and forgotten by others as a distinct clinical entity. Many do not realize that diagnosis can be made at an early stage. Furthermore, this disease is self-limiting in that the neuromuscular symptoms do not progress after a certain interval of time. Treatment, particularly surgical, of the deformities is effective.

Synonyms.—Peroneal muscular atrophy, primary peroneal atrophy, neural progressive muscular atrophy, peroneal form of progressive muscular atrophy, progressive hereditary neuropathic peroneal muscular atrophy, peroneal atrophy.

Definition.—This neuromuscular condition has been aptly described by Charcot and Marie[1] in 1886 as a "form of progressive muscular atrophy among family members occurring first in the feet and lower legs and later in the hands."

History.—In the middle of the nineteenth century, Aran,[2] Duchenne,[3] and Cruveilhier[4] reported cases they called progressive muscular atrophy. In the ensuing years, the muscular dystrophies were separated from the neural muscular atrophies. Eulenberg,[5] in 1856, and Friedreich,[6] in 1873, described progressive muscular atrophy. Similar descriptions followed in 1880 by Osler[7] and four years later by Ormerod.[8] Charcot and Marie[1] of France, and Tooth[9] of England published papers in 1886 describing at great length the clinical aspects of this disease. This confirmed the condition as a definite clinical entity. Charcot and his student, Marie, stated that the disease showed hereditary tendencies, involving first the feet and lower legs, later the hands and lower arms. "The muscles of the distal portions of the extremity were affected, whereas the axial group of muscles, such as the trunk, shoulders and face, maintained their integrity. The muscles undergoing atrophy showed fibrillary contractions. Sensation was usually intact, but at times some changes would be present. There were no pronounced contractures of muscles involved. Electrical changes of atrophying muscles and vasomotor disturbances of the involved extremities were evident."

Tooth thought the site of the disease was mainly in the peripheral nerves. He reported thirty-nine cases, thirty-six of which showed signs of the disease before 20 years of age. Since the original description, several authors have tried to subdivide this disease and to include other parts of the body, but these variations do not concur with the early concept of Charcot, Marie, and Tooth.

In 1899, Siemerling[10] reported a case that also had trunk involvement with diffuse and unequal atrophy. Sachs[11] described cases in which the infraspinatus muscle was involved, and Cavanaugh and Tucker[12] recorded

involvement of the supraspinatus. Roussy and Lévy,[13] in 1926, differentiated a familial type of clawfoot from muscular atrophy, but Symonds and Shaw[14] suggested that the clawfoot as described by the former was a delayed form of Charcot-Marie-Tooth disease. In 1929, Dawidenkow[15] related findings of combined involvement of the scapula and peroneal musculature. Since then, associated ocular manifestations have been reported such as unequal pupils, Argyll Robertson-like pupils, ocular palsies, ptosis, and optic atrophy.[16, 17, 18, 19] In recent years a combined form of Charcot-Marie-Tooth disease and Friedreich's ataxia has been noted.[20, 21]

Etiology.—The exact cause is unknown. A definite hereditary tendency is present, although a few isolated cases have been reported. This disease is commonly transmitted from one generation to the other, and there will be a variation in severity of the condition among members of the same or of different generations. A review of the literature reveals that cases of direct, indirect, dominant, recessive, and sex-linked transmission are possible.[22]

Incidence.—Considering the population as a whole, the condition is rather uncommon. There are cases of minimal severity that have never been brought to a doctor's attention. Of a yearly average of 12,000 patient visits to the Orthopaedic Dispensary of the Illinois Research and Educational Hospitals, only two to three new cases are diagnosed as Charcot-Marie-Tooth disease. These figures are subject to criticism so far as the over-all incidence is concerned. Macklin and Bowman[23] reported five generations involving 101 persons, twenty-one of whom showed peroneal atrophy. In a family, both sexes may exhibit equally the disease or there may be a preponderance of one sex over the other.

Pathology.—Virchow,[24] in 1885, reported histologic changes of gray degeneration in the posterior columns, particularly that of Goll. Recently, Schwartz[25] wrote that the spinal cord shows changes in the posterior columns, dorsal root ganglia, and ventral horn cells. The primary onset in the lower extremities may be explained by the fact that the longest axons usually suffer first in the degeneration of neuronic structures.

In addition to the findings of Schwartz, we have found that the nerve bundles exhibit a rather marked perineural fibrosis. The fibers show demyelinization and moderate degenerative changes in the axis cylinders. Furthermore, the blood vessels show no unusual microscopic changes. There are focal retrogressive changes in the muscle fibers varying in severity from the loss of staining qualities to the virtual complete disappearance of sarcoplasm. The nuclei remain as irregular pyknotic masses of chromatin. Replacement fibrosis is present in areas of severe muscular atrophy. The degenerative changes may affect a major portion of a muscle bundle, but scattered individual fibers remain. Adjacent muscle bundles appear entirely normal. There are no inflammatory cell infiltrations in these areas. Bone shows generalized atrophy. There is thinning of the cortex and the marrow spaces are mostly fatty. The cartilage of the joints is somewhat irregular and degenerated.

Diagnosis.—

History: The sequence of events begins with an insidious onset in child-

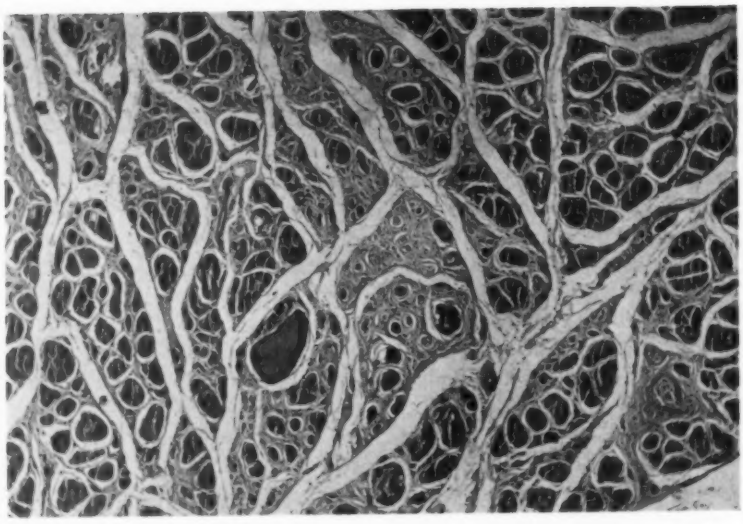

Fig. 1.—Note areas of degeneration in muscle. (Low power.)

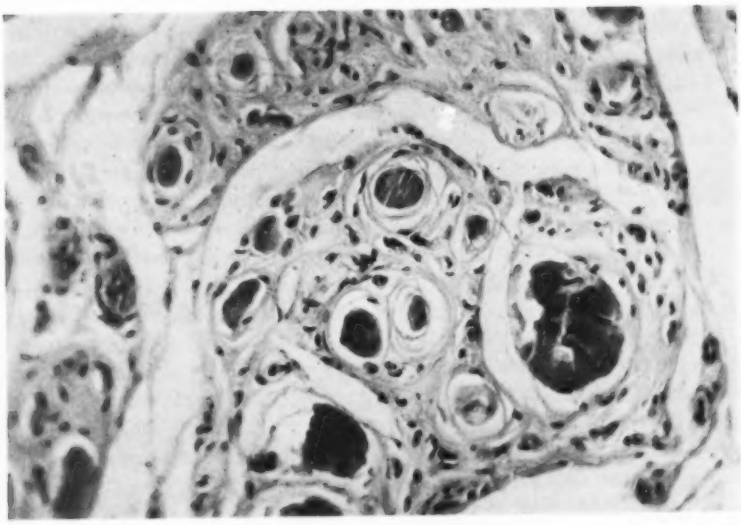

Fig. 2.—Replacement fibrosis of muscle is marked in some regions. (High power.)

hood or just before puberty. At first, the patient feels some instability in the foot described as a "repeated twisting or turning in of the ankle." The heads of the metatarsals depress, clawtoeing occurs, the longitudinal arch becomes more elevated, and this is accompanied by inversion of the foot. Painful callouses form under the heads of the metatarsals and also at the base of the fifth metatarsal. Pains develop from the mid- and forefoot and radiate into the leg. Later, a storklike deformity occurs with a drop foot of varying severity. A few years pass and weakness of the hands develops. Wasting of the thenar and then the hypothenar eminences occurs, and, in severe cases, a clawlike hand forms with contractures of the fingers. The patient has particular difficulty opposing the thumb to the remaining fingers. There is a decreased ability to discern light touch, pain, and temperature in the feet. This decreased sensory perception is not so pronounced in the hands. A positive family history makes the picture complete.

Examination: There is symmetrical involvement of the arms and legs. Pes cavovarus is present with a flattening of the anterior and lateral tibial compartments of the legs. The hands are not as extensively involved but show thenar flattening, and the thumb may be maintained in adduction next to the second metacarpal. The patient has a drop foot gait of varying severity. Measurements indicate atrophy of the foot to the knee and of the hand to the elbow. Sensory examination reveals blotchy areas of hypesthesia in the feet and hands. Perception of pain, temperature, and vibration is also decreased. The patellar and achilles reflexes are either absent or markedly depressed. The deep reflexes of the hand and forearm are similarly affected. No Babinski or Hoffmann reflex is present. Paralysis may be partial or complete of the muscle groups innervated by the common peroneal nerve, particularly the peroneus brevis and longus and the anterior tibial. Weakness is also present in the thenar group, and if the condition is very severe, the muscles innervated by the ulnar nerve in the hand also have decreased power.

Laboratory Studies.—The blood count, urinalysis, blood chemistry, spinal fluid, and x-rays of the spine are within normal limits. Spina bifida, if present, is thought to be an incidental finding. X-rays of the feet and hands show characteristic positional changes with accompanying bony atrophy. A reaction of degeneration is found. Polar reversal occurs with a marked hypoexcitability and the faradic response is nil. Another investigator[27] noted similar findings. The electromyogram reveals abnormal motor unit potentials of low voltage, and, in advanced cases, there are fibrillatory units as found in completely denervated muscle fibers.

Prognosis.—Prognosis is favorable in that the disease appears to be self-limiting. Progression ceases after the condition has been in existence for ten to fifteen years. The degree of involvement cannot be predicted. There is no influence on the duration of life.

Differential Diagnosis.—In classifying conditions in which there is a form of progressive muscular involvement, three categories can be employed (see Table I). The differential diagnosis should include other disorders. Dystrophia myotonica or myotonia atro-

phica[36] is an hereditary disease that has wasting in the sternocleidomastoid, facial, hand, and quadricep muscle groups, with associated bizarre findings as cataract and impotence. There is involuntary persistence of muscular contraction following voluntary initiation. The onset of the disease is usually between the ages of 20 and 30 years. Myotonia congenita or Thomsen's disease[37] is characterized by prolonged tonic contraction and retarded relaxation of muscles, both at the beginning and after voluntary movements. There is usually a positive family history, and the condition begins in early life. It is not associated with muscular wasting.

Myasthenia gravis[38] is a chronic disease with remissions and exacerbations. Head drop is an early sign together with weakness of the periocular and other facial muscles. Abnormal muscular fatigability is outstanding. Family periodic paralysis[39] is characterized by attacks of flaccid paralysis which develop abruptly and last from a few hours to a few days. The condition may first manifest itself when the child is 5 years old. Polyneuritis or peripheral neuritis,[29] present in all age groups, is a general term and is

TABLE I*

I. Primary Muscle Disorders—Primary Myopathies—Muscular Dystrophies	
A. Pseudohypertrophic muscular dystrophy[28, 29]	Enlargement of some muscles and wasting of others, especially thigh, calf, scapula, and shoulder.
B. Erb juvenile[30]	Hypertrophy and later wasting. Begins in arms and shoulders and then to trunk and lower extremities.
C. Landouzy-Dejerine[31]	Wasting only of fascioscapular-humeral areas.
There is restriction usually to the upper or lower extremities. The onset is in early life before puberty. Neither sensory changes nor reaction of degeneration are present. There is absence of fasciculation and no true neural involvement.	
II. Myelopathies—Amyotrophies	
A. Infantile form of muscular atrophy	
1. Amyotonia congenita (Oppenheim's disease)[33]	Extreme weakness and lack of tone without complete paralysis. At birth.
2. Progressive spinal muscular atrophy of Werdnig-Hoffman[34]	Onset at 6 months of age with death in few months to several years.
B. Progressive muscular atrophy—begins in adult life, feet rarely involved.	
1. Spinal form of Aran[2] and Duchenne[3]	Predominantly lower motor neuron. Atrophy begins in small hand muscles, then may spread to shoulder girdle and upper trunk.
2. Amyotrophic lateral sclerosis[32]	Combined involvement of lower motor neuron, corticospinal tracts, and cortical cells of Betz.
3. Progressive bulbar palsy[29]	Medullary innervated muscles primarily involved.
The muscular changes are secondary to upper or lower motor neuron changes. There may be a loss of motor power, atrophy, tremor, flaccidity or spasticity, and changes in electrical reaction such as complete reaction of degeneration. The deep reflexes are absent or hyperactive, depending upon the site of motor involvement.	
III. Neuritic Muscular Atrophies	
A. Dejerine-Sottas[35]	Onset in infancy. Peripheral nerves are enlarged. Positive family history.
B. Charcot-Marie-Tooth	
These conditions are mainly secondary to a peripheral nerve involvement.	

*Modified after Schwartz.

caused by endogenous and exogenous toxins, acute infections, and vitamin deficiencies. The muscles are painful and are tender to palpation, and there is usually a symmetrical flaccid motor weakness. Sensory impairment is more severe than in Charcot-Marie-Tooth disease.

In Friedreich's ataxia,[40] there is involvement of the posterior and lateral columns, the pyramidal and dorsal spinocerebellar tracts. The onset is usually between the ages of 2 and 15. The symptoms begin in the lower limbs and later the arms may be involved. Ataxia, loss of deep reflexes, impairment of deep sensibility, nystagmus, positive Babinski, and pes cavus are characteristic. Lower limb involvement is marked. In syringomyelia,[41] there is a lack of pain and temperature sensation with the preservation of touch. Muscular wasting and trophic changes are present especially in the upper extremities. Symptoms of pyramidal degeneration occur in the legs. Infantile paralysis[42] or anterior poliomyelitis shows an asymmetrical paralysis and muscular atrophy. The Guillian-Barré syndrome[42] is characterized by sudden onset and sensory as well as motor changes with albuminocytological dissociation in the spinal fluid.

Complications.—The outstanding complications of Charcot-Marie-Tooth disease are the deformities of the feet and hands. The extent of the deformity varies with the severity of the disease and may be such as to interfere with earning power. In the more severe case, the individual may become so handicapped so as to be unable to ambulate without crutches. In one instance, bilateral below knee amputation was done, and the patient is very pleased with the result.

Treatment.—There is some question regarding vitamins B and E[43] therapy. According to reports in the literature, for example, Eaton and others,[44] the patients have not been definitely benefited. The efficacy of medical treatment has been difficult to evaluate since the disease may halt at different stages of development. For mild cases, properly fitted shoes with inside metatarsal pads or metatarsal bars and an outside lateral lift would be in order. Efforts to resist impending contractures by manipulation and foot contrast baths also are helpful. The advanced cases should have foot reconstructive surgery. This consists of a plantar fasciotomy with a triple wedge arthrodesis, and, if indicated, scaphoidectomy. Adjunct tendon transplantation of some of the remaining functioning muscles can also be done in the feet[45] and hands. For very severe cases, amputation of the lower legs may be deemed necessary if for no other reason than to make the individual economically independent.

CASE REPORTS

The following cases are presented to show the variation in degree of involvement.

CASE 1.—B. P., a 12-year-old white male, was admitted to the Research and Educational Hospitals in March, 1945. His main complaint was difficulty in walking for two years. He said that both feet had been "turning in" and this had been associated with a repeated "twisting" of the ankles. Application of adhesive plaster gave him only slight relief. The outside border of his shoes showed excessive wear. One of his five brothers had similar foot trouble.

Examination revealed bilateral pes cavovarus with clawtoes. He walked on the lateral aspect of his feet with a halting gait. Atrophy was noted in

the anterior and lateral tibial compartments. Metatarsalgia and weakness of the anterior tibial, peroneus brevis and longus muscles were marked bilaterally. The plantar flexors were normal. Sensory examination indicated only a diminution of vibration perception in both feet. The achilles reflex was absent and the patellar, depressed. The superficial reflexes were intact and there was no positive Babinski.

Routine laboratory work was negative. X-rays showed a spina bifida occulta of the first sacral segment. Treatment consisted of a plantar fasciotomy and triple arthrodesis on the right and the same procedure with scaphoidectomy on the left. The patient did well, and three years later as he was being examined in the outpatient clinic, intrinsic atrophy and weakness of the hands, particularly thenar, were first noted.

CASE 2.—W. F., a 22-year-old white male, was admitted to the Research and Educational Hospitals in September, 1947. He complained of "turning in of both ankles" since the age of 12. He said that with the onset of above, clawing of the toes ensued, followed by increasing elevation of the longitudinal arches. Three years after the feet began to change, the hands became weak, smaller, and "shrunken."

Fig. 3.—B. P., 12 years of age. Note symmetrical involvement.

Both conditions, in the hands and feet, were progressive in severity until he was 19 years old. His mother had similar shaped feet.

Examination revealed involvement of both upper and lower extremities. There were cavovarus deformities of

both feet with hyperkeratosis along the lateral margins. Weight bearing was entirely on the outside of his feet. There was complete absence of function of the peroneus brevis and longus muscles and the anterior tibial muscle showed only a trace of movement. Atrophy was present in all muscles innervated by the superficial and deep peroneal nerves. Vibration sense was impaired and there were scattered areas of hypesthesia of the feet. Position sense was normal. There was marked atrophy and weakness of the thenar group of muscles, and to a lesser degree, the hypothenar. There was also weakness of the interossei and lumbricali muscles. The superficial reflexes were intact but the deep reflexes of the upper and lower extremities were absent. The Babinski reflex was absent.

Fig. 4.—W. F. Thenar atrophy is pronounced with adduction tendency of thumb.

The usual laboratory findings were within normal limits. Electrical studies showed altered responses to faradic and galvanic stimulation. This was consistent with a state of intact nerve supply associated with an hypoexcitability of both nerves and muscles. Electromyography confirmed the presence of intact motor units but there was damage to these units because of their inability to yield maximum voltages. There was no suggestion of a regeneration. X-rays revealed a spina bifida occulta of the first sacral segment.

Treatment consisted of bilateral plantar fasciotomies and triple-wedge arthrodeses. A muscle transplant was done because of the weak opponens action of the thumb. The flexor carpi ulnaris was utilized as the motor in the one hand, and, in the other, the flexor sublimis to the ring finger. The patient was pleased with his result and particularly with the newly found strength in his thumbs.

Case 3.—C. J., a 31-year-old white male, was admitted in April, 1945. His main complaints were painful callouses of both feet and weakness in the thumbs. When he was 8 years old, he noted the onset of a varus deformity in the right foot that was followed by the same deformity in the other foot several months later. The toes began to claw with the elevation of the longitudinal arches. He developed painful callouses under the heads of the first and fifth metatarsals. When he was 14 years old, weakness of the thumbs was first noted. Later on, he was unable to grasp objects between the end of the thumb and the other fingers. The condition of the feet has remained unchanged since 17 years of age. His maternal grandfather, two uncles, one aunt, and a cousin, as well as his mother, all have similar difficulty with their hands and feet.

Examination revealed the feet in marked cavovarus position with toes clawed. On walking, he stepped carefully and tried to bear most of his weight on the heels because of the painful callosities. There was complete absence of the peroneus brevis and longus and long extensor muscle action. There was marked atrophy of the lower legs to the knees. In both hands, there was no opponens action

in the thumb. Symmetrical atrophy of the hand and forearm was also present. There was diminished response to pinprick sensation in both feet and lower legs, but the vibratory and position senses were normal. The superficial reflexes were intact but the deep reflexes were absent in both the upper and lower extremities.

The laboratory findings were essentially negative. X-rays of the spine showed no deviation from the normal. Electrical examination revealed that fibrillatory potentials could be aroused mechanically by insertion of the needle into the right flexor pollicis brevis. There was also some low voltage motor unit activity. Faradic response was absent and, on galvanic testing, there was a very marked hypoexcitability with reversal of the polar formula.

A plantar fasciotomy and triple-wedge arthrodesis were done on the left side. The patient felt that the surgery improved the function of his foot; however, because of business reasons he was unable to remain and undergo further procedures.

CASE 4.—R. R., a 50-year-old white male, was admitted in January, 1945. His main complaint was deformities of both feet and hands which began when he was 3 years old. The "clubbing" of the feet was first noted and then was followed by changes in the hands. When he was 4 years old, plaster encasements were applied to straighten both feet without success. Since then, he has had no treatment. The deformities have not progressed since the age of 11. He could not recall similar changes in other members of his family.

Fig. 5.—C. J. Symmetrical cavovarus deformities.

Examination revealed marked involvement of all four extremities. The feet were in extreme cavovarus position with forefoot adduction. On walking, he bore weight on the caloused dorsal surface of the metatarsal-phalangeal joints. Thickened skin with underlying bursae was present laterally and over the dorsum of

Fig. 6.—R. R. Complete reversal of weight-bearing surface.

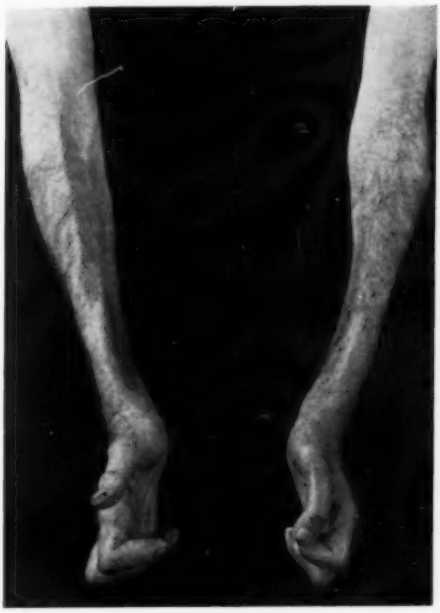

Fig. 7.—R. R. Extreme atrophy of hand and forearm.

the feet. There was overriding of the fourth toe by the fifth and of the big toe by the second. There was marked weakness in the anterior tibial, long extensor, and peroneus brevis and longus muscles with marked atrophy of the lower legs up to the knees. There was absence of the thenar eminence on both sides as well as the hypothenar on the left. This was accompanied by atrophy of the forearm muscles. The opponens muscle was nonfunctioning for either thumb and there was marked weakness in the remaining intrinsic muscles as well as the long flexors. There was scattered hypesthesia of the hands and feet as well as absent vibratory and position sense. The triceps and biceps reflexes were absent and the patellar and achilles jerks were markedly diminished. Further examination of the clawlike hands showed a flexion contracture of the fingers at the distal interphalangeal joints. The only remaining muscle action was the ability to flex the proximal interphalangeal joints about 30 degrees.

The laboratory findings were essentially normal. X-rays revealed no abnormal bony changes in the spine. Electrical studies showed other than electrical silence, fibrillatory potentials on mechanical stimulation. On faradic and galvanic testing, there was a good response from the median and radial nerves. There was no response from the ulnar nerve at the elbow and no response from the intrinsic muscles of the hands.

Because of the extreme deformities of both feet and since this was a great handicap to ambulation, bilateral below knee amputations were done. The patient was discharged with below knee prostheses. He was satisfied with the result and for the first time in many years was able to get along without crutches.

SUMMARY

A review of Charcot-Marie-Tooth disease is presented with illustrative cases. This condition can be differentiated from other neuromuscular conditions and diagnosed at a relatively early stage. It is self-limiting and surgery is of great help in restoring the affected individual to a more normal way of life.

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USE OF MILONTIN IN THE TREATMENT OF PETIT MAL EPILEPSY (THREE PER SECOND SPIKE AND WAVE DYSRHYTHMIA)

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In 1951, Zimmerman[1] reported on the use of methylphenylsuccinimide (Milontin†) in the treatment of petit mal epilepsy. He stated that this drug "is equal to, if not superior to, trimethadione (Tridione) in the therapeutic efficacy in the group studied and has the advantage of being relatively non-toxic." In 1952, Millichap[2] reported that "the efficacy of Milontin in the treatment of petit mal has been established by a controlled experiment." In thirteen of Millichap's twenty patients, toxic effects were encountered, and signs of glomerulotubular damage occurred in ten. The following report is a brief résumé of our experience with Milontin in the treatment of a small but selected group of patients, mostly children, who suffered with petit mal (simple staring) epilepsy.

MATERIAL FOR STUDY

Milontin was administered to twenty-one patients who suffered with frequent petit mal (simple staring) spells. We reserve the term petit mal for those spells which consist of transient lapses of consciousness associated with bilaterally synchronous three per second spike and wave forms in the electroencephalograms (Fig. 1). Bursts of spike and wave forms such as seen in Fig. 1 were present in essentially all of the 503 patients with petit mal (simple staring) epilepsy who were observed in our epilepsy clinic over a prolonged period of time.[3] One rarely encounters these abnormalities in the electroencephalograms of patients who suffer with other forms of epilepsy.

Nineteen of these twenty-one patients were between the ages of 5 and 14 years, the remaining two were over 15 years of age. Eight patients had previously been treated with other anticonvulsants, including Paradione and Tridione, without benefit; six with anticonvulsants, other than Paradione or Tridione, without benefit, and seven had had no previous therapy.

DURATION OF TREATMENT AND DOSAGE

The average duration of Milontin therapy was three to four months. Since all of our patients suffered with very frequent (daily) petit mal spells, this relatively short period of observation was deemed adequate.

The dosages of Milontin administered to our patients were similar to those advocated by Zimmerman. Treatment in each case was begun with 0.3 Gm., three times a day, and the dosage of the drug was increased gradually to a maximum of 3.0 Gm. daily. One of our patients increased the dosage on his own accord to 6.0 Gm. daily.

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†Milontin (N-methyl-a-phenylsuccinimide) was supplied to us through the courtesy of Parke, Davis & Company, Detroit, Mich.

RESULTS

The administration of Milontin did not control the spells in any of our twenty-one patients. In two patients, the number of spells was reduced to approximately one-half of the previous frequency. Thirteen of these patients were subsequently given either Paradione or Tridione and the spells were completely controlled in eight of them. The electroencephalogram also returned to normal in each of these eight patients.

No significant untoward reactions were observed in any of our patients during Milontin therapy. White blood cell counts and hemoglobin determinations were performed in each case at the time the therapy was begun and at monthly intervals thereafter. Monthly urinalyses were performed for eight of these patients.

DISCUSSION

Zimmerman reported that in twenty (68 per cent) of his twenty-nine patients with "pure petit mal" epilepsy, the spells were either completely controlled or markedly reduced in frequency with the administration of Milontin. No specific mention was made of the type of electroencephalographic pattern present in his patients. Millichap's twenty patients included ten patients with pure petit mal (pyknoepilepsy), five with "akinetic form of petit mal," and five with grand mal seizures combined with one

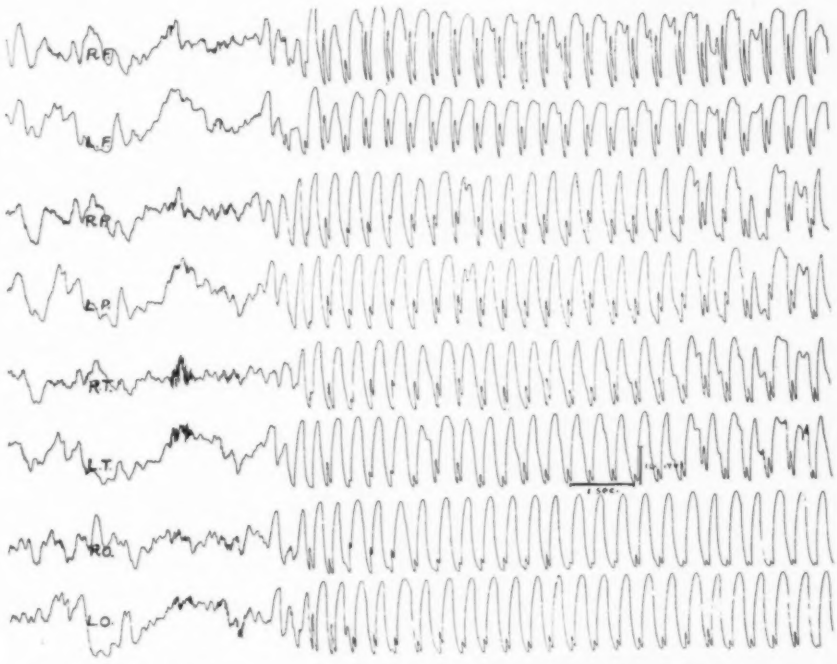

Fig. 1.—Burst of bilaterally synchronous three per second spike and wave forms in the electroencephalogram of an 8-year-old female who suffered with daily petit mal (simple staring) spells.

or both of "these types of petit mal." The classical spike and wave complex was present in the electroencephalograms of six of these patients. Millichap stated that "in 5 patients (26%) of the 19 in whom the effect of milontin could be assessed, the attacks were entirely controlled for at least five weeks, . . . there was a reduction of 80% or more in the number of attacks in 7 patients (37%), and in 4 (21%) the average reduction was 42%."

Our results with Milontin are obviously contrary to those reported by Zimmerman and Millichap. It is true that our patients consisted of a highly selected group. They were chosen to conform as closely as possible with Zimmerman's group of "pure petit mal." Zimmerman, however, did not correlate his clinical results with the electroencephalographic findings. Millichap reported that spike and wave forms were present in the electroencephalograms of six of his patients but he also did not make mention of any relationship between the clinical results and the electroencephalographic findings. He stated that the "effectiveness of milontin was related neither to the type of petit mal nor to the age of the patient."

In conclusion, our experience indicates that Milontin is essentially ineffective for the treatment of petit mal (simple staring) spells associated with three per second spike and wave forms in the electroencephalogram. We believe that the "dione" drugs (Paradione and Tridione) are the most effective anticonvulsants for such spells. In view of the findings of Zimmerman and Millichap, it may be that Milontin is of value in the treatment of other forms of epilepsy.

SUMMARY

Twenty-one patients with petit mal (simple staring) spells associated with three per second spike and wave forms in the electroencephalogram were treated with Milontin. The spells were not controlled in any of these patients. No untoward reactions were observed.

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POLIOMYELITIS IN THE NEWBORN INFANT

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IN THE course of studies on poliomyelitis in New York City,[1-5] attention was drawn to the occurrence of the disease in infants during the neonatal period. From 1949 to 1952 five such instances were found. They form the basis of this report. Three were in female infants with one death, and two in male infants, also with one death. Post-mortem examination of the two fatal cases showed tissue changes compatible with a diagnosis of poliomyelitis.

The clinical history of one of the babies has been published by Johnson and Stimson.[6] The baby was a full-term infant who appeared normal at birth but was found to have a bulging of the right side of the abdominal wall four days later. Weakness of the extremities followed. A spinal tap yielded a fluid which showed pleocytosis and increased protein content. Johnson and Stimson[6] believe that it is a case of congenital poliomyelitis. The mother had no manifest signs of the disease, but did have a respiratory infection with pain in the back and shoulders six weeks before. They suggest that this may have been poliomyelitis. The mother of one of the other babies (Case 1) developed acute poliomyelitis two days after delivery; another mother (Case 2) had poliomyelitis on the day of birth of her baby. A third mother (Case 3) developed poliomyelitis two days prior to delivery. In the last infant (Case 4) no history of illness in the mother could be elicited either during pregnancy or after delivery.

From the Bureau of Preventable Diseases, New York City Department of Health.

CASE REPORTS

CASE 1.—Baby M. A. O. (courtesy Dr. Samuel Barland). This female white infant was born at the Bethany Deaconess Hospital, full term, normal delivery on Aug. 10, 1949, with a birth weight of 3,856 grams (8 pounds 8 ounces). The mother, 26 years of age, became acutely ill on the second post-partum day, with paralysis of the right and lower left extremities. Spinal tap gave clear fluid with 400 cells per cubic millimeter, all lymphocytes. She was transferred to Queensboro Hospital on August 15.

On August 17, five days after onset of illness in the mother, her brother, 30 years of age, who lived in the same home, developed symptoms of an acute infection, and on August 20 showed paralysis of both lower extremities, abdominal masculature, and diaphragm. Spinal puncture yielded clear fluid with 165 cells per cubic millimeter, of which 96 per cent were lymphocytes. Death occurred on August 22, five days after onset of illness.

On August 20, the tenth postnatal day or eight days after onset of illness in the mother, the baby showed listlessness, pallor, and weakness of both arms. The temperature was 36.5° C. (98.1° F.). A spinal puncture yielded fluid with 150 cells per cubic millimeter; 70 per cent were red cells and 30 per cent lymphocytes. Blood count revealed 4,290,000 red cells, with hemoglobin of 103 per cent. White

cells were 12,800, with 35 per cent segmented forms and 12 staff forms; lymphocytes were 37 per cent and mononuclear cells 12 per cent. The infant's condition rapidly worsened and death occurred one day after onset, aged 11 days.

Post-mortem examination was made by Dr. Samuel Barland: *Brain and spinal cord:* Gross examination of the brain and spinal cord showed moderate swelling. The meningeal vessels were congested. Histologic sections were made only of the spinal cord. These showed changes in the anterior horns at the cervical level, with diminishing intensity of reaction in the distal segments. There were focal and diffuse infiltrations of inflammatory cells, predominantly polymorphonuclear neutrophils. In some areas, these cells were arranged in compact globular masses. Many ganglion cells showed various stages of degeneration in the form of chromatolysis and pyknosis. Minute areas of degeneration were present, but no hemorrhages. Reparative neuroglial proliferation was not observed.

CASE 2.—Baby J. J. (courtesy Dr. Walter Lehman and Dr. Philip J. Stimson). This white male infant was born at Brooklyn Hospital, full term, normal delivery on Oct. 28, 1949, with a birth weight of 2,520 grams (5 pounds 9 ounces). There were no immediate postnatal complications. The infant was fed once by the mother; thereafter, all feedings were given in the nursery.

The mother was 28 years of age. One week prior to delivery symptoms developed of an upper respiratory infection. Headache, muscle pains, nuchal rigidity, and fever of 39.3° C. (103° F.) occurred on the day of delivery. On the first post-partum day paralysis appeared of both legs and one upper extremity. Transfer to the New York Hospital was effected on November 4, the seventh post-partum day.

The baby was discharged home from the Brooklyn Hospital apparently well on November 4. He seldom cried, was lethargic, and had to be roused for feedings which caused choking. On November 7, at 10 days of age, the baby was seen by the family physician who noted no paralysis. On the following day, the baby was readmitted to Brooklyn Hospital, where examination showed a temperature of 37.7° C. (99.8° F.), lethargy, loss of muscle tone, and absent biceps and patellar reflexes. Respirations were regular, abdominal, and shallow. A feeding induced cyanosis and projectile vomiting.

Transfer was made to the New York Hospital. The infant was well developed, and had a temperature of 36.5° C. (97.7° F.), pulse 150, and respiratory rate of 40 per minute. The skin was clean, turgor good, with cyanosis of the hands and feet. The anterior fontanel did not bulge. There was a questionable left facial paresis. Painful stimulation and gagging induced no cry. Respirations were abdominal with slight intercostal activity; there were no supra- or infraclavicular retractions. The heart and lungs were normal. With exception of ankle jerks, all deep and superficial reflexes were absent. General muscle tone was poor. Plantar stimulation gave bilateral extensor responses. Rectal sphincter tone was poor. A spinal puncture yielded fluid containing 78 white cells per cubic millimeter, of which 90 per cent were polymorphonuclear. The spinal fluid sugar was 57 mg. per cent and total protein 164 mg. per cent. The urine showed a few red blood cells and several hyaline casts. Blood count showed a polycythemia of 7,200,000 red cells and hemoglobin of 22.5 grams. Differential count was within normal limits.

The baby was placed in oxygen with relief of cyanosis. His condition soon deteriorated. Cyanosis became more intense with each removal of infant from oxygen. Breathing was labored, with dilatation of alae nasae and use of accessory muscles of respi-

ration. The slight intercostal excursions quickly disappeared and costal retractions became evident. Abdominal distention was seen.

The following morning, examination of the heart revealed shifting to the left side of the chest. Atelectasis in the left lower lung was confirmed by fluoroscopic examination. Painful stimulation of right and left arms and left leg failed to evoke withdrawal responses. Slight withdrawal was present of the right leg. Progressive weakness ensued and respirations were feebler. There was no favorable response to stimulants and the Monahan respirator. The baby died about thirty-six hours after admission, November 10, aged 13 days.

It is difficult to state whether onset of illness in the baby began at 7 days of age or November 4, the date of initial discharge home, or at 10 days of age, November 7, the date when symptoms became apparent.

Post-mortem examination: Brain and spinal cord: The disease was severe and widespread, involving the entire spinal cord, medulla and midbrain, with evidence of encephalitis in the cerebral cortex. Grossly, there was diffuse congestion of the leptomeninges, with slight opacity in the arachnoid over the interpeduncular space. The choroid plexus of both lateral ventricles was also congested, with hemorrhage into the choroid plexus in both posterior horns. Section through the level of the cervical cord showed similar congestion of the gray matter of the anterior horns.

Microscopic examination revealed a cellular exudate of lymphocytes and a few granulocytes in the pia-arachnoid of the spinal cord and brain. A heavy exudate of lymphocytes, granulocytes, and large mononuclear cells was seen throughout the gray matter, and in lesser numbers in the white matter of the spinal cord, brain-stem, and midbrain. Few nerve cells of the anterior horns remained. There was also widespread destruction of nerve cells in the medulla and midbrain. The Beta cells were atrophic.

CASE 3.—Baby W. On Sept. 30, 1950, Mrs. K. W., 32 years of age, white, was admitted to the St. Mary's Hospital, Brooklyn, for delivery. On October 1 she complained of generalized muscle pains and had a temperature of 36.7° C. (100° F.). On October 3, two days later, she was delivered of her baby. On October 4 the mother showed paralysis of both lower extremities. A spinal tap yielded clear fluid containing 102 cells per cubic millimeter, predominantly lymphocytes, and having a total protein of 102 mg. per cent. The patient was transferred on October 4 for further care to Kingston Avenue Hospital, and subsequently to Sister Kenny Institute of Jersey City, N. J.

The infant was a full-term female, with a birth weight of 3,005 grams (6 pounds 10 ounces), who had no further contact with her mother after delivery. Progress appeared satisfactory until October 9, sixth postnatal day or eight days after onset of illness in the mother, when the baby became irritable, developed a temperature of 38.9° C. (102° F.), and showed paralysis of the right arm. Lumbar puncture was made on October 13, and showed a clear fluid with 55 cells per cubic millimeter, all lymphocytes. No organisms were seen either on smear or culture. A diagnosis was made of acute anterior poliomyelitis. On October 23 the baby was transferred to St. Charles Hospital, Brooklyn, for further care. On a follow-up visit to that hospital one year later, the baby was in good condition with mild paresis of the right arm.

CASE 4.—Baby N. J. C. This white male infant was born at full term at the Maimonides Hospital, Sept. 21, 1952. The birth weight was 3,147 grams (6 pounds 15 ounces). The mother, 22 years of age, was well throughout pregnancy. Her blood gave a negative reaction to the Kahn test. Other members of the family are the father and a 4-year-old sister, both well. No history could be

elicited of any illnesses among members of the household either during the mother's pregnancy or after the baby was brought home, nor was there any known exposure to poliomyelitis either in the maternity building of the hospital of birth or at home.

Labor proceeded normally and was of three and one-half hours' duration; the second stage lasted forty-six minutes. Delivery was assisted by episiotomy and forceps. The position was persistent occiput posterior. The mother's post-partum course in the hospital was uneventful. Her temperature course was normal.

Following birth the baby was cared for in one of the nurseries for newborn infants, and was given feedings of diluted evaporated milk modified with a carbohydrate. Occasional feedings were given by the mother in her room, when free movement was noted of the baby's arms and legs. Feedings were taken well; there was no vomiting, and the stools were of good consistency. There was no fever. On September 28, at the age of 7 days, weight 3,054 grams (6 pounds 12 ounces), the infant was circumcised. Following this procedure, the baby was discharged home. A note by the attending pediatrician stated that the infant was in good condition.

The baby made satisfactory progress until October 1, aged 10 days, when he became acutely ill with fever 39.1° C. (102.5° F.), and irritability. Feedings were refused; there was no vomiting or nasal regurgitation of food. Examination by a physician showed a red throat and a right lower extremity that was held extended at the knee and hip. Palpitation and passive movement caused increasing crying. A patellar reflex could not be obtained. There was no redness or swelling of the limb or of the joints. Nuchal spasm and bulging of the fontanel were absent. Oral penicillin was prescribed.

On the following day, October 2, the fever rose to 39.7° C. (103.5° F.). The baby was listless. No change was noted in the condition of the right lower extremity. A pediatric consultant was called and a diagnosis of possible osteomyelitis of the affected limb was entertained. Streptomycin in the dosage of 0.25 Gm. and 300,000 units of penicillin were given intramuscularly. Aureomycin was administered orally, 50 mg. every six hours. The next day the temperature was 37.8° C. (100° F.). The infant's condition remained the same. Streptomycin and penicillin were again given intramuscularly; oral aureomycin was continued.

On October 4 the temperature was 37.2° C. (99° F.); the mother noted that the baby did not move his left upper extremity. Examination disclosed a flaccid paralysis of the limb. The presence of an acute poliomyelitis was then suspected. Antibiotic therapy was discontinued. On October 10 spinal puncture was tried three

TABLE I. SUMMARY OF CASES OF POLIOMYELITIS OF THE NEWBORN INFANT, NEW YORK CITY, 1949 TO 1952

CASE NUMBER	NEWBORN INFANT	SEX	DATE OF BIRTH	ONSET OF POLIOMYELITIS IN MOTHER					ONSET OF ILLNESS IN BABY		DIED	
				PRENATAL		SAME DAY;	POSTNATAL					
				DATE	DAYS	DATE	DATE	DAYS	DATE	AGE (DAYS)	DATE	AGE (DAYS)
1	M. A. O.	f	8/10/49	—	—	—	8/12/49	2	8/20/49	10	8/21/49	11
2	J. J.	m	10/28/49	—	—	10/28/49	—	—	11/7/49	10	11/10/49	13
3	W.	f	10/3/50	10/1/50	2	—	—	—	10/9/50	6	—	—
4	N. J. C.	m	9/21/52	—	—	—	—	—	10/1/52	10	—	—
5*	W. W.	f	10/14/50	6 wk. prior	(?)	—	—	—	10/18/52(?)	4	—	—

*This case was reported by Johnson, J. F., and Stimson, P. J.: Clinical Poliomyelitis in Early Neonatal Period, J. PEDIAT. 40: 733, 1952.

times; each attempt yielded bloody fluid. Consultation with an orthopedist was then held for future therapy.

On October 21, at 30 days of age, the infant weighed 3,799 grams (8 pounds 6 ounces), and his general condition appeared good. Feedings were taken well, with no vomiting or nasal regurgitation. The left upper extremity showed a flaccid paralysis of the shoulder girdle area and a flail arm, forearm, and hand. The right lower extremity was narrower than the left and was held in a position of abduction and of slight flexion at the knee and hip. A minimal patellar knee jerk was present. There were no physical signs to suggest fracture or dislocation of the extremity.

DISCUSSION

The occurrence of only five cases of clinical poliomyelitis in infants during the neonatal period from 1949 to 1952, in a municipality the size of New York City, seems to indicate that the disease is rare during the first month of life. The five cases represent about 0.1 per cent of the 4,884 cases reported to the Department of Health in this period From 1949 to 1952 there were 639,018 live-births in New York City. The five newborn infants who exhibited signs of poliomyelitis represent a very low incidence rate. However, of the total group of mothers, seventy-two developed poliomyelitis prior to or shortly after birth of their babies, and three of these babies showed paralytic poliomyelitis. The vastly higher rate of poliomyelitis in infants born to mothers with an acute attack of poliomyelitis at about the time of delivery suggests a greatly increased risk in such infants. The number of cases is, however, too small to warrant conclusions.

Since 1897 there are recorded in the literature twenty-six instances of poliomyelitis during the first month of life.[7-24] Not all cases are well documented. The four additional cases described in this report bring the total to thirty. The diagnosis of poliomyelitis was based on history, physical examination, and confirmatory spinal fluid findings in fifteen of the cases. Of these, seven had post-mortem examinations and three successful transfer of the infection to monkeys. Two of the four cases reported by us (Cases 1 and 2) showed central nervous system changes compatible with a diagnosis of poliomyelitis.

Congenital Poliomyelitis.—There has been considerable controversy about the occurrence of intrauterine transmission of poliomyelitis. The statement is commonly made that the disease contracted by the pregnant mother will exert no influence on the baby. Up to 1953 a total of 610 cases of poliomyelitis in pregnant women has been reported in the literature.[25-27] Yet no proved instance of infection of the fetus has been noted.

There is evidence that passage of certain viruses can take place through the placenta. It has been demonstrated for one of the viruses of encephalitis, and for the viruses of measles, vaccinia, chickenpox, and lymphocytic choreomeningitis.[28] Recently, Bodian[29] and Horstmann[30] have shown that viremia is regularly present in the early stages of poliomyelitis in monkeys infected by feeding. Transplacental transmission of the virus of poliomyelitis has, however, not been demonstrated.

Of the reported cases of neonatal poliomyelitis, one described by Bas-

kin, Soule, and Mills[22] occurred three and one-half days postnatally, and one described by Johnson and Stimson[6] had a bulging of the right abdominal wall on the fourth day of life, possibly earlier. The case of Frovig[18] showed signs of poliomyelitis on the fifth day of life. No other reported cases have been detected so early. Whether these are or are not instances of congenital poliomyelitis is speculative. Case 3 in our series represents a newborn baby whose mother had poliomyelitis two days prior to delivery. The infant had no contact with her mother after birth, nor did she have contact with any other person who had symptoms of poliomyelitis. Yet the infant developed manifest signs of the disease six days after birth. Was the infant infected in utero?

Passive Immunity.—Aycock and Kramer[21] have shown that the relative infrequency of poliomyelitis in infants under 1 year of age is due in considerable measure to passive transmission of immune bodies through the placenta. Neutralization tests indicated a correspondence of immunity between urban mothers and their newborn babies in ten out of twelve (83 per cent) of those tested. This immunity is transitory. Active immunity develops gradually with advance of age, as a result of contact with the virus of poliomyelitis, so that most adults are immune. The age at which the maximum percentage of individuals develops immunity to poliomyelitis varies according to the density of population of a community and the degree of exposure. In more populated areas, where there is crowding and primitive sanitary conditions, immunity is acquired at earlier age levels. Paul and his associates[32] in Cairo demonstrated this rise in titer of antibodies to each of the three types of poliomyelitis virus in children from ages 1 to 4 years when 70 to 100 per cent possessed such antibodies.

SUMMARY

During the four years, 1949 to 1952, five cases of acute paralytic poliomyelitis in newborn infants occurred in New York City. The histories of four of these cases are presented. The fifth case was previously reported by Johnson and Stimson.[6] There were two deaths. During the same span of years, 4,884 cases of poliomyelitis were reported to the department of health. The incidence of manifest poliomyelitis during the neonatal period was therefore about 0.1 per cent. Three of the mothers had poliomyelitis; one on the day of delivery; one, two days prior to delivery; and one, two days after delivery. The chance of developing poliomyelitis in the neonatal period appears to be greater among infants born to mothers with poliomyelitis. Transmission of infection may possibly occur in utero.

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EFFECT OF PENICILLIN INJECTIONS DURING ACUTE POLIOMYELITIS

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SINCE 1950 there has been widespread interest in the relation between the occurrence of paralytic poliomyelitis and previous injections of various substances, including antigens, penicillin, and other medications. Most of the numerous articles which have appeared in the American and British literature have concluded that there is a definite relation between the site of paralysis and the site of injection.[1, 2, 3] Injections of immunizing substances within the two months immediately preceding the onset of polio seem to be chiefly implicated. Some authors, however, seem to feel that penicillin injections are also related to the occurrence of paralysis, including injections given during the few days immediately preceding the onset of poliomyelitis.[4, 5]

A study was made of the relation between the occurrence of paralysis and the injection of penicillin during the acute illness of poliomyelitis patients admitted to the Elizabeth Kenny Institute in Minneapolis during the calendar years 1950 and 1951. The determination of the number of penicillin injections was made on the basis of the history and the hospital chart. All cases were excluded in which the history was in any respect indefinite regarding the number of penicillin injections. Less than 10 per cent of the total cases had to be excluded for this reason.

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Determination of the occurrence of paralysis was made by members of the staff of the Physical Medicine Department of the Elizabeth Kenny Institute. Each patient was examined one or more times by a physiatrist, and a complete analysis of muscle function was made. If this examination showed weakness of any degree in any of the gluteal muscles, the patient was included in the group having paralysis. In some instances, patients who were admitted in critical condition were too sick to undergo detailed muscle analysis, and died without any such examination. Such patients were not included in the study if the chart did not contain a clear statement as to the presence or absence of function in the lower extremities. Less than 5 per cent of the cases had to be excluded for this reason. Apart from these cases and those previously mentioned who did not have unequivocal histories regarding penicillin injections, all patients admitted during 1950 and 1951 and diagnosed as having acute poliomyelitis were included in this study. The total number of cases used was 385.

RESULTS

Of the 132 patients who showed some degree of weakness in one or more of the gluteal muscles, sixty-six had received penicillin injections and sixty-six had not. The patients who did not develop gluteal weakness numbered 253, of which 123 had received

penicillin and 130 had not. These data are presented in Table I.

TABLE I

	PENICILLIN	NO PENICILLIN
Gluteal paralysis	66	66
No gluteal paralysis	123	130

The application of the Chi-square test of significance to this table reveals that the slight differences between the penicillin and the no penicillin groups are entirely without statistical significance ($p > .70$).

Another way to study the effect of penicillin injections is to take only those patients receiving penicillin and to determine whether the number of injections is related to the occurrence of gluteal paralysis. Table II summarizes the results of such a study.

TABLE II

	NUMBER OF PENICILLIN INJECTIONS	
	1 TO 5	6 OR MORE
Gluteal paralysis	20	46
No gluteal paralysis	35	88

Here it will be seen that slightly more than one-third of the patients receiving up to five injections had gluteal paralysis, with twenty showing some degree of weakness and thirty-five with normal gluteal muscles. A similar ratio obtains among the patients receiving six or more injections—forty-six with paralysis and eighty-eight normal. There seems to be no significant relation between the number of injections and the occurrence of paralysis, for the Chi-square test gives a p of greater than .70.

In tabulating the cases for this study, separate totals were made for 1950 and 1951, and the tables derived from them were subjected to the same statistical analysis as is here reported for the two years combined. Since precisely similar results were obtained they are not presented in detail.

DISCUSSION

The data show clearly that the injection of penicillin during the acute stage of poliomyelitis does not produce paralysis of the muscles into which it is injected. This is in marked contrast to the relation which seems fairly well established between the site of antigen injections and paralysis. It may be that this discrepancy is to be explained in terms of the different nature of the substances injected.

The time relation between the injection and the acute illness may also explain the difference between the present results and those concerning antigen injections. The antigen injections occurred well before the onset of the poliomyelitis. For up to two months after the injection, the injected limb seemed to be somewhat more vulnerable to poliomyelitis. The penicillin injections considered in the present study were all given during the acute illness. It may well be that a certain period is required for some local tissue reaction to occur before the injected region will become more susceptible to paralysis. If this is true, the minimum period required must be at least five days, for many patients included in the present study received one or more injections of penicillin in the first day or two of an illness that was nonspecific at the onset. Paralysis began on the fourth to the sixth day during the second portion of the biphasic temperature curve. The present data do not yield any suggestions

as to which of these two explanations is correct, and indeed neither one may be.

SUMMARY

In a study of 385 polio patients admitted during 1950 and 1951 to the Elizabeth Kenny Institute, no relation was found between paralysis occurring in gluteal muscles and injection of penicillin during the acute illness.

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A CLINICAL STUDY OF NEUROBLASTOMA

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WE HAD the privilege of observing an unusual case of neuroblastoma for several years. Although the case began as a very malignant tumor which could not be removed surgically, the patient is alive and well today. This stimulated us to analyze the other cases of neuroblastoma at the Roswell Park Memorial Institute and the Buffalo Children's Hospital. We were deeply impressed by the lack of response to treatment and the early fatal outcome in most of the cases studied.

Twenty-one cases of neuroblastoma were collected. One case that has been under observation since 1936 is presented in detail. The remaining twenty cases are briefly summarized.

CASE REPORTS

CASE 1.—P. S., R.P.M.I. No. 29879, B.C.H. No. 41955.

The following case of neuroblastoma is one which we were privileged to observe since July, 1936. The patient is now alive and well but has a large calcified mass in the left abdomen. This cure may have been due to irradiation, or the tumor may have undergone a change from the immature cell to a mature cell with intratumoral hemorrhage, necrosis, and calcification. When the infant was 10 months of age, the mother discovered a mass in the left upper abdomen which increased rapidly in size (Fig. 1). One month later, hematuria and abdominal pain developed. The child was admitted to the Buffalo Children's Hospital and retrograde pyelography (Fig. 2) revealed a large mass in the region of the left kidney. There was marked caliectasis of the left upper kidney. The soft tissue mass extended to involve the upper pole. A transperitoneal exploratory operation (July 30, 1936) revealed a nonremovable tumor of the left kidney. Biopsy material was interpreted at that time by two different pathologists as Wilms' tumor. The first course of x-ray therapy was given at the Buffalo Children's Hospital from Aug. 8, 1936, to April 29, 1937. The factors were 140 KVP (H.V.L. 0.5 mm. Cu); skin target distance, 40 cm.; port, anterior left and mid-abdomen from tip of zyphoid to groin (exact measurements not available). Treatment was given in increments of 100 r on Aug. 8 and 18, Sept. 2 and 28, Nov. 3, 9, 16, and 26, Dec. 14 and 21, 1936, April 8, 15, and 29, 1937. The total surface dose was 1,300 r and the total dose at 5 cm. depth (tumor mass) 800 r. On Nov. 25, 1936, a second attempt to remove the tumor failed.

The child was admitted to the Roswell Park Memorial Institute on Aug. 31, 1937. Physical examination revealed a large nodular tumor occupying the left abdomen. Although ascites was present, no evidence of distant metastases was demonstrable.

Treatment consisted of 200 KVP irradiation (H.V.L. 0.9 mm. Cu) given through an anterior, posterior, and lateral field. From Aug. 31, 1937, to Jan. 5, 1938, a total of 5,772 r was delivered to the tumor by daily increments ranging from 66 to 132 r.

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During the course of treatment, there was slow but steady improvement. The tumor regressed in size and two months after irradiation therapy the ascites had disappeared. X-ray films of the abdomen revealed complete calcification of the tumor which continued to feel hard and nodular. The patient gained weight and felt well, but in September, 1939, another course of irradiation treatment was given, since renewed activity of the tumor was suspected because of anorexia and weight loss.

Fig. 1.—Patient at 10 months of age, prior to treatment. Note large abdominal mass.

From Sept. 11 to Oct. 27, 1939, 200 KVP (H.V.L. 0.9 mm. Cu) radiation was employed, and a total of 1,760 r was delivered to the tumor, using an anterior and a posterior field with daily increments of 94 r. On Nov. 27, 1939, the patient had gained one pound. There was still a hard calcified mass in the left abdomen which had not changed in size. No other tumefaction was palpable. In January, 1947, when almost 12 years of age, the patient began menstruating. Her general physique was that of a girl of her age (12 years). On palpation of the abdomen, there was still a hard, fixed nodular tumor felt, which occupied a large part of the left upper abdomen. A flat film of the abdomen revealed no change in the size and shape of the calcified tumor, and a barium enema showed no displacement or encroachment on the transverse or descending colon.

Fig. 2.—Retrograde pyelogram at 10 months of age before the first course of treatment.

On Jan. 13, 1950, intravenous pyelography was done (Fig. 3). The thirty-minute film revealed normal structure in the collecting system on the right side. The left upper pole showed caliectasis. The pelvis and ureters were not visualized. The lower two-thirds and perirenal tissue was occupied by a calcified mass. Hypoplasia of the lower dorsal and

lumbar vertebrae, left hemipelvis, and proximal left femur were noted. The epiphyseal centers of ossification of the iliac crest had appeared bilaterally.

The pathological material removed by biopsy in 1936 and then interpreted as Wilms' tumor of the kidney has recently been re-examined. The present diagnosis is neuroblastoma. A description by Dr. K. Terplan, pathologist, is as follows: "Re-examination of the material received,

Fig. 3.—Excretory urogram taken when patient was 14½ years. This is eleven years after the last course of irradiation. Note the large calcified tumor mass with evidence of function in the superior calyx of the left kidney.

which consists of fibrous and fat tissue surrounding a small lymph nodule, shows that we are unquestionably dealing with a malignant neuroblastoma and not with a Wilms' tumor. There is localized calcification within the tumor." (Figs. 4 and 5.)

At present the patient is alive and well. Her general physical condition is excellent. On Aug. 30, 1952, she was 17 years of age. This patient represents a fifteen-year cure following irradiation alone.

CASE 2.—P. D., B.C.H. No. 119102. A 16-month-old white male was admitted on June 20, 1947, with a history of a fall three weeks prior to admission. He gradually lost the ability to walk, and a fever was present.

Physical examination revealed a left shift of the trachea. The reflexes were sluggish. A chest x-ray showed a mass in the upper posterior third of the right lung. The diagnosis of neuroblastoma was established by means of a needle biopsy of the lung lesion. The child was given four injections of nitrogen mustard consisting of 1 mg. each, and this was supplemented with 1,200 r over the lung area. The immediate response was good and the patient was discharged on July 14, 1947. A chest x-ray on Aug. 27, 1947, showed marked regression of the lung lesion and the child's general condition was improved. The child was readmitted for further nitrogen mustard and external irradiation. Two intravenous injections of 1.4 mg. each were given and 2,400 r was directed over the chest area in twelve days. The child was discharged on Sept. 10, 1947, showing marked improvement. A chest x-ray on Aug. 20, 1951, was reported as negative. The child is alive and well at present. This tumor was thought to arise from the upper thoracic sympathetic chain.

CASE 3.—J. F., B.C.H. No. 144656. A 2½-year-old white male was admitted on May 12, 1930, with symptoms of otitis media, neck rigidity, inability to walk, and fever. Examination revealed a right preorbital swelling, strabismus, right exophthalmos, and a mass in the left upper quadrant. There was a small tumor over the right temporal area. X-ray showed a calcified mass in the left upper quadrant and destruction of the right ileum. Retrograde pyelograms

Fig. 4.—Photomicrograph of an abdominal lymph node removed during the second exploratory operation in 1936. Note the typical arrangement of the neuroblasts in rosette fashion. (×200.)

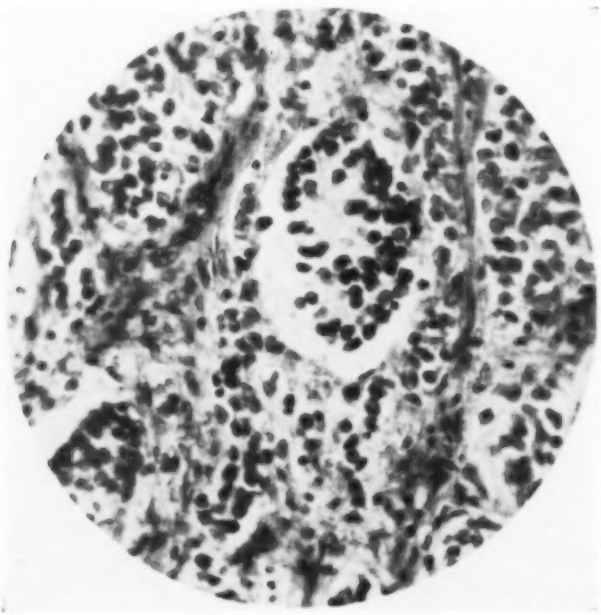

Fig. 5.—Photomicrograph high power, showing the detailed pattern of the neuroblastic cells forming a typical rosette. (×900.)

showed a mass above and behind the left kidney with displacement of the left kidney. There was good renal function bilaterally. A scalp nodule was removed and was reported as a malignant neuroblastoma. The child's course was rapidly downhill and he expired July 28, 1930. An autopsy revealed a large neuroblastoma above the left kidney with metastases to the right ileum, skull, abdominal lymph nodes, and to a right undescended testicle.

CASE 4.—R. T., B.C.H. No. 144076. A 2½-year-old male was admitted on Feb. 27, 1951. The presenting symptoms were anemia, malnutrition, fever, cough, and anorexia. A palpable mass was noted in the left upper quadrant and this was firm and nodular with extension into the pelvis. Intravenous pyelograms showed deformity of the left renal calyces and a diagnosis of a Wilms' tumor of the left kidney was made. A chest x-ray and roentgenogram of the bony structures were reported as negative. On March 3, an exploratory operation of the left kidney was undertaken and a large adherent mass was found that could not be removed. A biopsy was taken and the pathologist reported a malignant neuroblastoma. The renal tissue was compressed but not invaded. On March 4 external irradiation was begun and 1,400 r was given over the left renal area. Nitrogen mustard was given on March 23. The patient received little if any benefit from the x-ray or nitrogen mustard therapy and expired on July 16, 1951, after a rapidly downhill course.

CASE 5.—J. C., B.C.H. No. 144658. A 5-day-old white male was admitted on July 30, 1926, with complaints of passing small amounts of dark urine associated with pain. The abdomen was markedly distended with large dilated veins. The infant was jaundiced and a large palpable mass was found in the right abdomen with extension into the pelvis. X-rays were not obtained. The child's course was rapidly downhill and he expired on Aug. 4, 1926, six days after admission. No therapy was given. An autopsy showed a large neuroblastoma of the right adrenal with extensive liver metastases.

CASE 6.—M. N., B.C.H. No. 144659. A 2½-year-old white male was admitted on Sept. 21, 1936. The presenting complaints were loss of weight and anorexia. Examination revealed two large abdominal masses. One was thought to be liver and the other spleen. X-ray showed two areas of rarefaction in the skull, one in the right upper humerus and two in the right upper femur. A diagnosis of Gaucher's disease was made and the child was sent home. The patient expired at home on Nov. 10, 1936, after a rapidly downhill course, and an autopsy at home revealed a neuroblastoma of the right adrenal with extensive abdominal and liver metastases.

CASE 7.—J. B., B.C.H. No. 153304. An 8-year-old white male was admitted on April 5, 1950, with complaints of weakness, anemia, pain, and loss of motion of left lower extremity. There were small tumor masses under the skin on the forehead. A mass was palpable in the right upper quadrant. X-rays revealed a calcified mass in the right abdomen and rarefaction of the pelvis, femur, skull, and ribs. Treatment consisted of external irradiation to the skull and abdominal area and four injections of nitrogen mustard, each dose being 2 mg. On May 9 the right kidney and mass were removed. The pathological report was malignant neuroblastoma of the right adrenal. On May 20 another course of nitrogen mustard was given consisting of 2 mg. I.V. for four days. The scalp lesions regressed slowly under treatment but never completely disappeared. The patient expired at home on Nov. 5, 1950.

CASE 8.—J. G., B.C.H. No. 163718. A 14-month-old white female was admitted on Jan. 25, 1951, with com-

plaints of wheezing, shortness of breath, and fever. The abdomen was distended with dilated vessels. A large, firm, fixed mass was palpable in the right upper quadrant. X-rays showed a large diffusely calcified mass in the right upper abdomen. The chest x-ray and roentgenogram of the bones were negative. On Jan. 27, 1951, an exploratory operation was performed and a large, fixed mass involving the aorta and vena cava was found but could not be removed. A biopsy was taken and the pathologist reported a malignant neuroblastoma of the right adrenal. The child expired on the first postoperative day.

CASE 9.—R. A., B.C.H. No. 167219. An 8-month-old white male was admitted on April 27, 1951, with complaints of difficult breathing and inability to move the lower extremities. Examination revealed impaired resonance of the right chest, and loss of motion of the lower extremities. X-ray of the chest showed a large calcified tumor mass in the posterior mediastinum and erosion of the sixth, seventh, and eighth ribs. A right thoracotomy was done on May 5, 1951. The right chest was filled with tumor, which could not be removed. A biopsy was taken and the pathologist reported a neuroblastoma of the right dorsal sympathetic chain. The patient expired on the eleventh postoperative day without further treatment.

CASE 10.—T. D., B.C.H. No. 85934. A 20-month-old white male was admitted on March 3, 1943, with complaints of anorexia, fever, and increase in the size of the abdomen. A large mass was palpable in the right abdomen. Retrograde pyelograms showed a filling defect of the right kidney pelvis and a diagnosis of Wilms' tumor was made. On April 3, an exploratory operation was undertaken and a large adherent tumor was found which could not be removed. A biopsy was taken and the pathologist reported malignant neuroblastoma of the right adrenal. The patient expired at home on July 1, 1943.

CASE 11.—N. S., B.C.H. No. 94861. A 17-month-old white female was admitted on Aug. 10, 1944, with symptoms of fever, anorexia, and inability to walk. Examination revealed a distended abdomen and a large mass in the right upper abdomen. Intravenous pyelograms show displacement of the right kidney downward by a large mass. On Aug. 22, 1944, an exploratory operation was performed and the patient expired during surgery. An autopsy revealed a malignant neuroblastoma of the right adrenal with metastases to the skull, liver, and lung.

CASE 12.—V. S., B.C.H. No. 68643. A 5½-year-old white male was admitted on Jan. 7, 1940, with complaints of joint pain and fever. Examination revealed multiple painful joints and anemia, and a diagnosis of rheumatic fever was made. X-rays of the spine, chest, heart, and sinuses were normal. The child was treated with salicylates and transfusions. The patient's course was rapidly downhill. An autopsy showed a malignant neuroblastoma of the right adrenal with metastases to the liver, lungs, pancreas, bone marrow, and lymph nodes.

CASE 13.—H. S., B.C.H. No. 90497. A 4-year-old white female was admitted on July 24, 1944, with complaints of progressive enlargement of the abdomen associated with pain and anemia. A mass was found in the right abdomen. This was firm and nontender. Enlarged lymph nodes were palpable in the left neck and both axillae. The abdominal veins were distended. Retrograde pyelograms showed a filling defect of the right kidney pelvis. A diagnosis of Wilms' tumor was made preoperatively and a right nephrectomy was performed on August 9. The pathologist reported a malignant neuroblastoma of the right adrenal with involvement of the right kidney. The

child received three x-ray treatments of 100 r each over the right kidney area, but expired on Aug. 15, 1944, on the sixth postoperative day.

CASE 14.—J. T., B.C.H. No. 154056. A 7-year-old white male was admitted on April 22, 1950. One month prior to admission a mass was noted in the abdomen associated with neck lumps and anorexia. Examination revealed bilateral palpable supraclavicular nodes and a tender mass in the mid upper abdomen. X-ray of the chest showed mediastinal widening and nodulation. A flat x-ray of the abdomen showed a calcified mass in the left upper quadrant. A biopsy of the supraclavicular nodes was done and the pathologist reported a malignant neuroblastoma. Nitrogen mustard was administered and high-power x-ray was begun to the mediastinal region. Nitrogen mustard 2.3 mg., was given I.V. for four days. On May 8, a chest plate showed the mediastinal lesion to have regressed. Exploratory operation was done on May 23, and a large inoperable tumor was found replacing the left adrenal gland with extension across the midline. A second course of nitrogen mustard consisting of 2.3 mg. I.V. for four days was given and the patient showed temporary improvement. Stilbesterol, 2.5 mg. b.i.d., was given with little if any response. The patient developed metastatic bone lesions and expired on Dec. 8, 1950.

CASE 15.—D. E., B.C.H. No. 139785. A 3½-year-old white female was admitted on March 3, 1949. She complained of right conjunctival irritation and increased tearing of the right eye for three weeks prior to admission. Ten days before admission an enlargement and protrusion of the right eye was noted. Examination revealed a protruding right eye with a dilated pupil. The child was afebrile. X-ray showed haziness of the right orbit. Intravenous pyelograms were reported as negative. On March 7 an incision was made over the right eyebrow and very friable tissue was removed. The pathologist reported a malignant neuroblastoma. Treatment consisted of external irradiation from March 9 to 30 and 20,000 r were given over the right orbit. Nitrogen mustard was given for four days consisting of 1.5 mg. daily. The orbital swelling progressed and on May 27 the right eye was removed. On August 1 a radical resection of the orbit and eyelid was performed. A chest x-ray on October 24 showed multiple pulmonary metastases. The child lived for two years and expired on Nov. 6, 1951. An autopsy revealed tumor in the right adrenal, lungs, base of brain, and pituitary gland.

CASE 16.—K. J., B.C.H. No. 94937. A 10-year-old white female was admitted on Aug. 23, 1944. She complained of a stiff neck, fever, listlessness, and pain in her back and shoulders. Examination revealed a ptosis of the right eyelid, bulging of the upper right chest, and tracheal displacement to the left. The lower extremities were drawn upon the abdomen. Tubercular meningitis and poliomyelitis were considered. X-ray showed a mass in the upper right chest. A needle biopsy of the chest lesion was done and the pathologist reported a malignant neuroblastoma. The patient had a rapidly downhill course and expired on Sept. 2, 1944, five days after admission. An autopsy was not obtained. The tumor was thought to arise from the thoracic sympathetic chain.

CASE 17.—K. B., B.C.H. No. 174210. A 3½-year-old white male was admitted on Nov. 13, 1951, complaining of multiple joint pains, fever, and ptosis of the left eyelid. Examination revealed ptosis of the left eyelid and an associated left exophthalmos. X-ray showed rarefaction of the pelvic bones and femur. Intravenous pyelograms showed slight downward displacement of the left kidney. The patient expired on Dec. 7, 1951, and an autopsy showed neuroblastoma of the left adrenal gland with metastases

to the liver, abdominal lymph nodes, bones, and brain.

CASE 18.—M. E., B.C.H. No. 152457. A 3½-year-old white female was admitted on Dec. 15, 1951, with pain in the right upper abdomen, anorexia, and constipation. Examination revealed a palpable liver, several areas of skin pigmentation, and fever. X-ray showed rarefaction of the skull and humerus and calcification of the right adrenal. Intravenous pyelograms showed downward displacement of the right kidney with an associated hydronephrosis. A bone marrow aspiration biopsy showed multiple rosettes, and the pathologist reported a malignant neuroblastoma. On December 21 an exploratory operation was performed and a large right adrenal tumor with extension into the liver was found. A biopsy was taken and this was reported as malignant neuroblastoma. The patient was given high-power x-ray and nitrogen mustard. The course was downhill and she expired on March 4, 1952.

CASE 19.—J. H., R.P.M.I. No. 71372. A 19-year-old white female was admitted on March 16, 1951, complaining of pain in the right lower quadrant. A right nephrectomy had been done on Aug. 14, 1950, because of gross hematuria and a palpable right flank mass. The pathological report was that of a malignant neuroblastoma. Examination revealed a well-healed right flank incision and palpable right inguinal nodes. A right inguinal node was removed on March 20, 1951, and the pathologist reported a metastatic neuroblastoma. High-power x-ray was begun on April 2, 1951. The factors were 250 KVP (H.V.L. 2.5 mm. Cu); port, anterior right abdomen, posterior right abdomen, and lateral right abdomen. Treatments were given in increments of 150 r daily for 36 days for a total tumor dose of 5,148 r. The response was good. Other external irradiation was given as follows: July 5 to 20, 1951, for 16 days. The factors were 250 KVP (H.V.L. 2.5 mm. Cu); ports, right lower abdomen. Daily increments of 300 r were given for a total tumor dose of 3,600 r. On November 20 to December 14 another course was given. The factors were 250 KVP (H.V.L. 2.5 mm. Cu); ports, anterior right abdomen, posterior right abdomen, and lateral right abdomen; daily increments of 150 r for a total tumor dose of 4,467 r. The right inguinal adenopathy disappeared; however, in February, 1952, a right lower quadrant mass was noted and this has slowly progressed in size. The patient's general condition is good. She is asymptomatic and works daily.

CASE 20.—R. K., R.P.M.I. No. 73798. A 12-year-old white male was admitted on Dec. 28, 1951. Following a football injury to the right eye on Oct. 18, 1951, there was marked swelling of the right upper eyelid and brow associated with a proptosis of the right eye. A diagnosis of abscess was made and an attempt at incision and drainage was done. During this procedure the ophthalmologist encountered tumor tissue and secured a biopsy. A report of malignant neuroblastoma was received, and the boy was referred to this institution for therapy. Examination revealed a proptosis of the right eye with extensive soft tissue swelling about the right orbit. He had marked cervical lymphadenopathy. X-ray of the skull and chest, and intravenous pyelograms were reported as negative. High-power x-ray was begun on Jan. 2, 1952. The factors were 250 KVP (H.V.L. 2.5 mm. Cu); ports, medial and lateral right orbits. A daily increment of 122 r was given for 22 days for a total tumor dose of 3,808 r. External irradiation was also given over the right neck and face, the mediastinum, lateral left chest, and anterior abdomen. The patient's course was rapidly downhill and he expired on March 21, 1952. An autopsy showed metastases to the abdominal lymph nodes, pancreas, bowel, and lungs.

CASE 21.—K. M., R.P.M.I. No. 74878.

A 1½-year-old white female was admitted on May 9, 1952, with complaints of loss of weight and a progressive enlargement of the abdomen of two months' duration. Examination revealed an emaciated child with a large, firm, palpable mass in the left upper quadrant. Intravenous pyelograms showed a deformity of the left renal collecting system and downward displacement of the left kidney. A diagnosis of Wilms' tumor was made and an exploratory operation of the left kidney was undertaken on May 10, 1952. A large tumor mass replacing the left adrenal and involving the left kidney was found. There was extension across the midline of the abdomen and the aorta and inferior vena cava were encircled by tumor. A biopsy was taken and the patient was closed without further surgery. The pathologist reported a malignant neuroblastoma. The child expired on the second postoperative day.

INCIDENCE

Neuroblastoma is one of the most frequent retroperitoneal malignant tumors in infants and children. In this series of twenty-one cases the primary tumor occurred in several areas of the sympathetic nervous system. Ten tumors were primary in the right adrenal. There were six involving the left adrenal. The remaining source of primary tumors were: thoracic sympathetic chain, 2; right kidney, 1; dorsal sympathetic chain, 1; and unknown, 1. The sex incidence is almost equal. In our series there were twelve males and nine females. The youngest individual was 5 days old and the oldest, 19 years of age, with an average age incidence of 4.3 years.

ETIOLOGY

Neuroblastoma was first described by Virchow[1] in 1864 and classified as a glioma. In 1891 Marchand[2] concluded that histologically there was an association between the developing sympathetic nervous system and certain of the adrenal tumors. Wright[3] in 1910 was studying the suprarenal tissue of embryos and recognized the similarity of these cells to those of the neuroblastoma and concluded that their origin must be from the sympathetic nervous system. By far the greatest number of reported neuroblastomas have their origin in the medullary portion of the adrenal gland; however, they may and do arise from any portion of the sympathetic nervous system. The adrenal medulla is ectodermal in origin and according to Wiesel[4] the formative cells, sympathogonia, from which the adrenal medulla develops, begin to invade the anlage of the cortex during the eighth embryonic week. The sympathogonia emanates from the neural crest and migrates forward to give origin to the chromaffin (pheochromoblast) and ganglia cells (sympathoblasts) of the adrenal medulla and sympathetic nervous system. Willis[5] states that, "According to Poll the development of ganglion cells from sympathogonia continues until the tenth year. Theoretically then, neuroblastic tumors could arise at any time prior to the tenth or twelfth year of life, though we might expect the majority to do so during the fetal or infantile period when cellular proliferation is most vigorous."

PATHOLOGY

According to Willis[5] the neuroblastoma consists of immature cells which proliferate at the embryonic or formative level and never reach the differentiated quiescent state. In the neuroblastomatous tissue, as in fetal

sympathetic ganglion, the first recognizable stage in neuron differentiation is the appearance of rosette-like clusters of cells around small central zones of fine nerve fibers.

Microscopically the predominant cells are undifferentiated nerve cells which are the formative cells of the sympathetic nervous system and the adrenal medulla. These tumors are very cellular and the cells are small with round nuclei rich in chromatin and resemble lymphocytes. The cytoplasm is characteristically scanty with delicate fibrils of varying length. Mitotic figures are numerous and the presence of rosettes or pseudorosettes is characteristic. Grossly the tumors are usually of considerable size and show a tendency to hemorrhage, degeneration, and calcification. Another feature of many of these tumors is the frequent invasion of neighboring structures, thus making complete removal very difficult or impossible. Occasionally if the tumor is encountered early it may be encapsulated and easily enucleated; however, with growth, extension to surrounding organs occurs rapidly.

SYMPTOMATOLOGY

In most of these cases, the presenting symptoms were vague and of a general character. Fever, loss of weight, anorexia, anemia, and joint pains were often observed. Pain and loss of power of the lower extremities were seen. Some cases presented an abdominal mass. Others presented nodules on head or orbital symptoms as exophthalmos or ptosis of lid. Although several children appeared quite well except for the local orbital change, the majority of the children appeared to be quite ill. They were pale and listless. Most of the presenting symptoms could be ascribed to the early metastases of the highly malignant and rapidly spreading tumor.

DIAGNOSIS

The diagnosis was very difficult in most of these cases. This was especially true in the group of cases which presented anemia, fever, anorexia, and joint pains as the initial symptoms. Rheumatic fever, tuberculosis, and Wilms' tumor were among the initial diagnoses. When anemia, fever, anorexia, and loss of weight are present with pain and loss of power of the lower extremities, one must be suspicious of neuroblastoma with metastases.

When an abdominal mass is present, together with nodules on the scalp or orbital changes, the diagnosis is much easier.

In those cases which presented an abdominal mass without evidence of metastases, it was quite difficult to differentiate between an adrenal neuroblastoma and a Wilms' kidney tumor. In some cases it is impossible to determine preoperatively which tumor is present. It may be impossible to diagnose the tumor until the pathologist reports.

Intravenous pyelograms, biopsy of accessible tumor tissue, bone marrow aspiration, and x-rays of the skeletal system and lungs have aided in diagnosis.

Intravenous pyelograms are of distinct value. They usually visualize well. The kidney may be pushed downward by the enlarged adrenal. Occasionally the kidney pelvis will be deformed enough by the external pressure so that a Wilms' tumor cannot be excluded. The neuroblastoma sel-

dom invades the kidney, but in one of these cases there was invasion of the kidney and it acted like a renal tumor. Perirenal air insufflation was not done in any of these cases. The procedure was considered dangerous in this type of tumor because of its vascularity. X-rays of the skull, chest and pelvis, and long bones were routinely done for metastases which occur early and widely. These tumors are so rapidly growing that necrosis, hemorrhage, and calcification are fairly frequent. Areas of calcification in the tumor are a distinct aid in diagnosis. Biopsies were obtained from any available areas of tumor. These were usually diagnostic and showed the typical embryonal nerve cells of the sympathetic nervous system, arranged in pseudorosette formation. Biopsies were obtained from scalp nodules, the orbital cavity, supraclavicular lymph nodes, and bone marrow. Bone marrow aspiration is of definite value. Two obscure cases were diagnosed by this method. A slide of one is shown (Fig. 6). These show the wide spread of the malignant cells of this rapidly growing tumor. Bone marrow aspiration is of value in diagnosis and also in prognosis. A bone marrow which shows many tumor cells gives a very bad prognosis. Bone marrow aspiration also gives an indication of the response to treatment. Several cases under treatment were followed by multiple bone marrow aspirations to note the number and distribution of tumor cells.

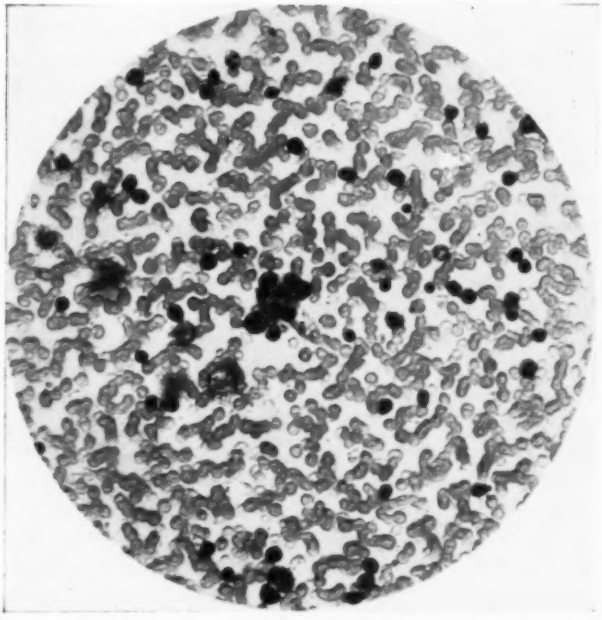

Fig. 6.—Photomicrograph of a sternal bone marrow aspiration smear. This shows the clumps of neuroblasts among the red blood cells. (×900.)

TREATMENT

These cases apparently fall into several groups. In the group which entered the hospital with general symptoms of anemia, anorexia, and joint pains, multiple metastases were often present and treatment was of no avail. These cases pursued a rapid downhill course in spite of transfusions, nitrogen mustard, irradiation, and surgery.

Treatment may be of some help in the case presenting as an abdominal mass without evidence of metastases. The tumor cells in these cases may be a more mature type and with less tendency to invade. In this type of case, early surgery with subsequent irradiation offers the best hope. Only an occasional patient will be saved, however, as the surgery of neuroblastoma is exceptionally difficult. Although the surgery was performed by different skilled and experienced surgeons, in none of the cases was it possible to remove the tumor entirely. While the tumor is somewhat encapsulated, there is a local direct spread to the surrounding tissues. Direct growth into the liver, vertebral column, and diaphragm is common. Large metastatic and adherent lymph nodes are encountered. There is direct extension across the midline, surrounding and compressing the aorta and vena cava. It was very difficult to identify these major vessels in several of these cases. Because of the local infiltrative character of these tumors, it is apparent that only an occasional one will be successfully removed. An encapsulated tumor with more mature cells offers that chance.

These patients were treated with surgery, multiple transfusions, nitrogen mustard, and irradiation. There was some improvement temporarily in some cases but the fatal outcome was only delayed.

PROGNOSIS

The prognosis of malignant neuroblastoma is very bad. Most of our patients pursued a rapid downhill course to death. Treatment was of little help. Apparently, at this time, there is very little help for the child presenting itself with multiple metastases from a neuroblastoma, composed of rapidly growing embryonal sympathetic nerve cells. These cells are widely disseminated before the mother tumor can be identified. The only chance of cure appears to be in the encapsulated tumor with no metastases and composed of more mature cells. There are three survivals among the twenty-one cases. One patient has survived fifteen years and can be listed as a cure. Another patient has survived five years, five months, and at present is alive and well without evidence of disease. The third patient has lived one year eight months since the diagnosis was established. This 19-year-old female is alive and well at present. However, there is a palpable right lower quadrant mass which is progressing in size and unquestionably represents metastatic disease. The average survival rate of the entire series is sixteen months. Two or 10.5 per cent of the twenty-one cases survived five or more years.

CONCLUSION

From a review of the twenty-one presented cases, we feel that there is no adequate therapy for the neuroblastoma composed of immature cells. These malignant cells spread widely and rapidly and the metastases rendered the outlook hopeless. Early surgery and irradiation are helpful

in neuroblastomas composed of more mature cells. These tumors are more encapsulated and tend to remain localized. Bone marrow aspiration is of definite value both for diagnosis and prognosis. Nitrogen mustard offers very little in the therapy of this disease. When anemia, fever, loss of weight, and a palpable abdominal mass are present in an infant, one must be suspicious of neuroblastoma. This lesion is the most common retroperitoneal malignant tumor in infants and early childhood.

SUMMARY

A brief outline of the incidence, etiology, pathology, symptomatology, diagnosis, prognosis, and treatment of neuroblastoma is presented.

One case observed since 1936 is reported in detail. Twenty additional cases are summarized.

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SPINAL CORD TUMORS IN CHILDREN

A Review of the Subject and Presentation of Twenty-One Cases

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STUDY of the records of twenty-one patients with intraspinal neoplasms treated at Childrens Hospital during the past twenty-two years has brought to our attention certain interesting and instructive problems created by these tumors, and considered worthy of recording. This material comprises patients ranging from 5 months to 14 years of age, whose symptoms were due principally or exclusively to neoplasm within the spinal canal. Known congenital tumors and intraspinal implants from cerebral growths have been excluded (see Case 4). While tumor in three cases may have arisen from bony elements of the vertebral column, signs of neurological disturbance were far more prominent and important than those attributable to bone destruction, rendering these patients eligible for inclusion in the series. We wish in this report to appraise our own experiences and to review the work of others concerning the many difficulties associated with tumors of the spinal cord in infancy and childhood.

FREQUENCY AND PATHOLOGIC NATURE

Intraspinal neoplasms in children have been reviewed by a number of authors, and various important characteristics of clinical and pathologic nature are recorded.[7, 12, 17, 20] In two exhaustive reviews of the world literature, Hamby[15, 16] presented data on 214 patients less than 15 years old with intraspinal tumor, pointing out, as had others, that pathology of cord tumors differs percentage-wise between childhood and adult groups. Glioma and extradural sarcoma (both generally unfavorable for surgical treatment) were the commonest types, with congenital tumors, neurofibroma, and meningioma next in frequency. In adult life, neurofibroma is generally considered to be the commonest cord tumor, with meningioma second, and glioma third in order of frequency.[10, 14] Hamby observed that meningioma was rarely recorded in a patient younger than 12 years, and that neurofibroma was uncommon in younger children. Sarcoma was noted in all age groups, but glioma was rare before the age of 4 years. As might be expected, lipoma, dermoid, and other congenital tumors were much more common in the earliest years of life, a finding supported by Mosberg,[19] who noted that 17 of 23 reported cord tumors in infants less than one year were congenital.

Spinal cord tumors are much less frequent before the age of 15 years than in adult life; Bailey[21] estimated a ratio of 1 cord tumor to 20 brain tumors in the younger group, contrasted to 1 to 6 ratio in adults. At Los Angeles Childrens Hospital 164 children under 14 years of age with brain tumors were observed during the

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twenty-two year period which yielded 21 intraspinal tumors, a ratio of approximately 1 to 8. The spinal tumors comprised 9 gliomas, 3 neurofibromas, 3 sarcomas, 3 hemangiomas, 2 neuroblastomas, and 1 cystic anomaly of the filum terminale (see Table I). In one of our glioma cases post-mortem examination showed widespread ependymoma implants throughout cerebral and spinal subarachnoid spaces, and within the third ventricle. This case is included in the series because the patient had extended history of spinal cord impairment and no sign suggesting intracranial tumor until shortly before death. It was not possible at autopsy to determine which of the many tumors constituted the primary lesion. The cystic anomaly occurred in a boy 4½ years old and was classified as representing heterotropic nerve tissue, a developmental variant accompanying spina bifida occulta. However, the solid stalk of this cyst had microscopic appearance very similar to ependymal glioma (Fig. 1), and primary neoplasm of the filum terminale has not been excluded from consideration.

CLINICAL FEATURES

Just as there are pathologic variations with age groups, the clinical syndrome produced by intraspinal tumor in a child tends to differ considerably from that ordinarily described for adults. This is attributable in many instances to youth of the patient and his inability to accurately describe minor numbness and weakness of extremities or impairment of sphincter control. Ingraham[18] pointed out that the examiner must be always alert to the possibility of cord tumor in a child with weakness of the lower extremities, pain in spine or legs, or any ill-defined state suggesting the chance of spinal cord disease. This very pertinent suggestion is worth repeated emphasis.

That tumor of the spinal cord in children as well as in adults need not produce early objective neurological signs such as weakness or numbness of extremities was first reported by Bennett.[2] He described four patients with

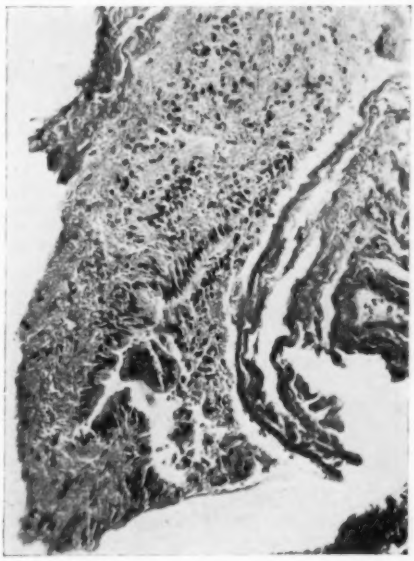


Fig. 1.—Case 6. This lesion consisted of a thin-walled cyst extending downward in continuity with the conus medullaris, and terminating in a firm stalk attached to the anterior wall of the spinal canal at the first sacral vertebra. Cyst contained spinal fluid, and almost filled the lumbar spinal canal, markedly displacing cauda equina roots. Figure shows cross section of the stalk which presumably represents an enlarged filum terminale, and contains an irregular ependymal cell-lined canal. Ependymomas are prone to develop in those areas of the central nervous system where ependymal cells of this type are found. (Hematoxylin and eosin, ×430.)

subsequently proved spinal cord tumor in whom back and spinal root pain plus spasm of back and hamstring muscles persisted for several years before any neurological signs were ob-

TABLE

PATIENT AGE	SEX	TUMOR TYPE AND LOCATION	EARLY SYMPTOMS	DURATION OF SYMPTOMS BEFORE DIAGNOSIS	IMPORTANT FINDINGS	TENTATIVE DIAGNOSES
M. B. 10 yr. Case 1	M	Ependymoma conus and cauda equina $T_{12} - L_5$	Leg pain. Urinary incontinence	27 mo.	Weakness lower limbs. Saddle anesthesia. Absent knee and ankle jerks	Pott's disease? Tumor of spine?
B. C. 12 yr. Case 2 Previously reported[20]	M	Ependymoma extramedullary and cauda equina $T_8 - L_4$	Back and leg pain	2 yr.	Stiffness and kyphosis, lower back. Slight weakness legs. Knee and ankle jerks diminished	"Stiff back"
J. B. 11 yr. Case 3	M	Ependymoma cauda and conus $T_{12} - L_4$	Leg pain. Backache, nocturia	13 mo.	Increased lumbar lordosis, stiffness of lower back. Hamstring spasm	Postpoliomyelitis syndrome
F. A. 6 yr. Case 4 Previously reported[20]	M	Ependymoma spinal and cerebral, numerous implants intra- and extramedullary	Stiffness back and legs, pain in back	14 mo.	Stiff neck and back. Hamstring spasm. Unequal knee jerks	Poliomyelitis
B. J. 13 yr. Case 5 Previously reported[20]	M	Intramedullary ependymoma (?) (poorly differentiated) T_6	Back pain, numbness right leg and foot	3 mo.	Neck flexion caused back pain; neck compression caused epigastric pain; slight saddle numbness; calves atrophic	Spinal cord tumor
W. H. 4½ yr. Case 6	M	Intradural cyst continuous with conus, extending to L_4 with solid stalk. Heterotopic nervous tissue? Ependymoma (?) (Fig. 6)	Stiff back, shuffling gait, leg pain	7 mo.	Back stiff; lumbar flattening. Hamstrings tight. Left knee and angle jerk diminished. Left thigh and calf smaller than right	Postpolio syndrome? Retroperitoneal tumor?
R. S. 2½ yr. Case 7	F	Astrocytoma Grade II $C_3 - C_6$	Stiffness and pain in neck	2 mo.	Stiff neck, unable to extend. Hyperactive knee and ankle jerk	Neck sprain. Spinal cord tumor?
J. M. 2 yr. Case 8	F	Astrocytoma intramedullary $C_5 - T_4$	Stiff neck, stumbling gait ? weak left arm	9 mo.	Stiff neck; flexion and extension poor	Cervical fracture? Disc herniation?
M. R. 11½ yr. Case 9	F	Spongioblastoma (?), intramedullary and extramedullary $C_6 - L_4$	Pain in legs mainly at night. Slow micturition	3 mo.(?)	Anesthesia below T_8, hypesthesia $T_4 - T_8$. Total paraplegia. A reflexia in legs	Transverse myelitis
R. C. 10 yr. Case 10	F	Intramedullary glioma, not microscopically verified $T_9 - L_4$	Impaired gait, constipation	6 mo.	Weakness and atrophy legs, impaired sensation below T_2 (?)	Spinal cord tumor

TABLE I

SPINAL PUNCTURE AND FLUID	X-RAYS	OPERATIVE PROCEDURE	RADIATION THERAPY	RESULT
Not done	Erosion pedicles and vertebral bodies (no myelogram) (Fig. 5)	Incomplete removal of tumor in cauda equina	2,000 r (measured in air) 135 KVP 25-day interval	18 yr. later paraplegic self-employed (Fig. 6)
Complete block, xanthochromic fluid, clotting	Marked pedicular erosion in earliest x-rays. Lipiodol block L_3 (Fig. 3, *A* and *B*)	Partial removal tumor	3,000 r (air) 200 KVP 37-day interval	1950: (9 yr. postoperatively). No symptoms, no abnormal findings
Partial block, xanthochromic fluid. Protein 1,000 mg. %	L_3 interpedicular space widened. Pantopaque block L_3	Subtotal removal not including intramedullary tumor in conus	No	Present. 16 mo. postoperatively, no neurological defect. Spine stiffness persists
Dry lumbar taps (previous cisternal tap: 57 mg. % protein)	Negative (no myelogram)	Partial removal tumor in cauda equina	No	Died 2 mo. postoperatively. Autopsy
Protein 570 mg. %	Plain films normal. Lipiodol block T_7	Partial removal tumor	No	Developed paraplegia. Died 4½ yr. postoperatively
Normal	Minor spina bifida occulta Pantopaque defect $L_1 - L_2$	Removal cyst and portion of terminal stalk	No	Present, 16 mo. later: no symptoms, no abnormal findings
Block uncertain. Protein 230 mg. %	Pantopaque block C_5 Plain x-rays: Loss normal lordosis	2-stage with myelotomy. Partial removal tumor	No	Essentially unchanged. (Now 5 mo. postoperatively) except neck stiffness and pain relieved
Block probable. Protein 181 mg. %	Widened interpedicular spaces $C_4 - T_4$. Pantopaque block at T_4 (Fig. 2)	Myelotomy and partial removal of tumor	No	Neck stiffness persists. Mild weakness legs (2 mo. postoperatively)
Block. 900 cells, 89% polys. Xanthochromia 4+ Pandy	Reported normal (no myelogram)	Partial removal tumor $T_2 - T_7$	No	Total paraplegia. Died 1 mo. postoperatively. Autopsy showed tumor $C_6 - L_4$
Complete block, light xanthochromia. Protein 1,500 mg. %	Plain films reported negative. (Discarded) Lipiodol block L_1	Biopsy	3,000 r (air) 200 KVP 36-day interval	10 yr. later paraplegic; decubitus ulcers. Bedfast

TABLE I—

PATIENT AGE	SEX	TUMOR TYPE AND LOCATION	EARLY SYMPTOMS	DURATION OF SYMPTOMS BEFORE DIAGNOSIS	IMPORTANT FINDINGS	TENTATIVE DIAGNOSES
S. M. 11 yr. Case 11	M	Extradural round-cell sarcoma $L_4 - S_2$	Leg pain, urinary incontinence	1 yr.	Left foot weak. Legs atrophic. Hypesthesia below L_3 ankle jerk decreased	Postpolio syndrome
M. D. 9 yr. Case 12	F	Extradural sarcoma L_5 involving vertebra (later metastatic)	Leg pain. Urinary frequency	6 wk.	Flexed posture of legs. Urinary incontinence. Saddle anesthesia	Tumor of vertebra
M. B. 6½ yr. Case 13	F	Extradural sarcoma (Ewing's) $L_2 - L_3$	Leg pain. Back stiffness	6 wk.	Absent knee jerks and ankle jerks. Stiff thoraco-lumbar spine. Weakness feet	Postpolio syndrome
C. F. 14 yr. Case 14	M	Extradural capillary hemangioma, involving also body of T_6 vertebra	Numbness of feet. No pain	1 mo.	Slight weakness legs. Hypesthesia below T_8, saddle spared. Ankle and knee jerks hyperactive. Babinski signs	Same as final diagnosis
P. C. 14 yr. Case 15	F	Hemangioma T_8 vertebral body (x-ray diagnosis)	Weakness of legs	1 mo.	Congenital heart disease. Spastic weakness legs. Partial anesthesia below T_8	Thrombosis spinal artery
B. H. 5 mo. Case 16	F	Extradural hemangioendothelioma $T_7 - T_{12}$	Weakness of legs. Urinary dribbling	3 wk.	Paraplegia. Anesthesia to T_{10}. Relaxed anus	Spinal cord tumor
L. W. 13½ yr. Case 17	F	Intradural neurofibroma L_2	Back pain and stiffness	1 yr.	Rigid back below T_{10}	Hysteria? Possible tumor or intraspinal cyst
R. J. 12 yr. Case 18	M	Neurofibroma intradural, cauda equina	Pain right leg, retention urine on one occasion	3½ mo.	Hamstring spasm, pronounced. Neck compression caused pain right sacrum and buttock ankle jerk absent	Cauda equina tumor
J. V. 19 mo. Case 19	M	Extradural neurofibroma (hourglass) with abdominal extension. $T_6 - T_{12}$	Difficulty walking	6 mo.	Waddling gait. Mass left posterior chest. Sensory and motor status normal (?). Low thoracic kyphosis	Tumor of spine
T. B. 7 mo. Case 20	M	Neuroblastoma extradural $T_8 - L_3$	Irritability. Disinclination to sit up	2 wk.	Complete paraplegia. Anesthesia of lower limbs. Relaxed anal sphincter	Spinal cord tumor
G. B. 10 mo. Case 21	F	Neuroblastoma, extradural $T_{11} - L_3$ and hourglass intra-abdominal extension	Weakness of legs	3 wk.	Weakness lower extremities. Stiff spine. Abdominal mass	Poliomyelitis

TABLE I—CONT'D

SPINAL PUNCTURE AND FLUID	X-RAYS	OPERATIVE PROCEDURE	RADIATION THERAPY	RESULT
Protein 140 mg. %	Erosion sacrum (evident in earliest x-rays)	Partial removal tumor	3,000 r (air) 200 KVP 29-day interval	Developed paraplegia. Died 19 mo. postoperatively
Protein 81 mg. %	Compression body of L_5	None	3,450 r (air) 200 KVP 36-day interval	Died 3 mo. after onset. Autopsy: widespread metastases
Complete block, xanthochromic 2,100 mg. % protein	Mild concavity L_3, L_4? Compression L_2, enlarged IV foramina L_{23}, L_{23}, cisternal myelogram: block at L_2	Partial removal tumor	10,400 r (air) 200 KVP 27-day interval	No change in neurological status. Pain relieved. (Now 2 mo. postoperatively)
Complete block. Protein 260 mg. %	Consistent with hemangioma body of T_6 vertebra	Partial removal extradural tumor	3,000 r (air) 200 KVP 27-day interval	Present, 14 yr. later, no symptoms, no abnormal findings
Protein 200 mg. %	Striation body of T_8 vertebra (no myelogram)	None	1,200 r (air) 200 KVP 13-day interval	Legs improved. Died 1 yr. after onset. (Rupture brain abscess)
Not done	Pronounced erosion pedicles $T_7 - T_{12}$	Subtotal removal tumor	1,200 r (air) 200 KVP 20-day interval	Died 6 wk. postoperatively. No autopsy
No block (3 taps). Protein 1,165-3,710 mg. %	Plain films normal. Lipiodol block L_2	Removal tumor	No	Present, 15 yr. later, no symptoms except slight stiffness of back
Block. Protein 532 mg. %	Reported normal (no myelogram)	Removal tumor	No	Present, 16 yr. later, slight numbness right perineum. Back slightly stiff
Block. Pandy 4+ Xanthochromia	Marked erosion rib ends and pedicles $T_6 - T_{12}$ (Fig. 4)	Laminectomy, partial removal tumor. Laparotomy, abdominal mass inoperable	No	8 yr. later total paraplegia; otherwise reasonably well
Xanthochromic. Protein 4,000 mg. %	Kyphosis and scoliosis at L_1. Pantopaque block L_2	Subtotal removal	3,000 r (air) 200 KVP 22-day interval	6½ yr. later. No neurological defect except mild sphincter paresis. Kyphoscoliosis
Block. Fluid xanthochromic protein 1,600 mg. %	Erosion 9-11 ribs L_2, L_2. Intervertebral foramina enlarged	Decompressive laminectomy; partial removal tumor	3,200 r (air) 200 KVP 50-day interval	5 mo. postoperatively. Abdominal mass smaller. Legs possibly stronger.

served. It was stressed that such a situation may be not uncommon, yet tragically misdiagnosed in its earlier stages, a prediction which has since been supported by numerous authors,[1, 5, 8, 9, 22] and is borne out by our patients. Common erroneous diagnoses include hysteria, congenital lordosis or scoliosis,[13] tuberculous spondylitis, herniated intervertebral disc,[22] multiple sclerosis, postpoliomyelitis syndrome, or intra-abdominal tumor or disease, leading at times to protracted therapy with back braces and postural exercise, or even to corrective orthopedic operations, exploratory laparotomy, psychoanalysis, or other equally elaborate and inappropriate measures.

Conversely, intraspinal tumor of either malignant or benign variety may manifest itself abruptly, causing rapidly increasing weakness and numbness of parts below the tumor level, thereby being confused with transverse myelitis, Guillian-Barré syndrome, apoplexy of the cord, or epidural abscess. On occasion cord tumor produces a syndrome suggestive of acute anterior poliomyelitis with fever, stiffness of the neck, and pleocytosis of spinal fluid.[6] Differentiation of these two conditions may be difficult, particularly in an infant or young child, but if tendon reflexes in paretic lower extremities are normal or increased in volume, neoplasm must be considered a more likely diagnosis than poliomyelitis.[3]

In our series, the combination of spine and leg pain with or without stiffness and limitation in motion of the neck or back was described by thirteen patients, and formed the commonest group of presenting symptoms. Pain was often more pronounced at night, and coughing and sneezing almost invariably caused radiation into the arms, trunk, or legs; in three patients restriction of back movement was considered to be more troublesome than spontaneous pain. Duration of symptoms in this group of thirteen patients was difficult to establish precisely but ranged from five weeks to approximately two years; objective weakness and numbness of lower extremities were slow to appear (over one year) in at least four patients, and during this interval abnormal reflexes or other remarkable neurological signs were not noted. In four other cases diagnosis of space-taking intraspinal lesion was established by spinal fluid examination and myelography, although sensory, motor, or reflex abnormalities were never clearly demonstrated.

Onset of illness was of varied character in the remaining eight patients not included above. Four were less than 2 years of age and were brought to the hospital because of irritability and fretfulness, plus progressive weakness in the lower limbs of rather sudden onset, accompanied in one instance by fever. Weakness, numbness, and diminution or loss of tendon reflexes in the legs led to early suspicion of cord tumor. Three older children described progressive loss of sensation and strength in the legs of two weeks to six months' duration without noteworthy pain, and examination in each case showed a distinct level, below which there were deficiencies in sensory and motor function, suggesting the correct diagnosis in all without undue delay. One patient (Case 4), finally shown at operation and post mortem to have wide dissemination of ependymoma throughout cranial and spinal subarachnoid spaces, became ill

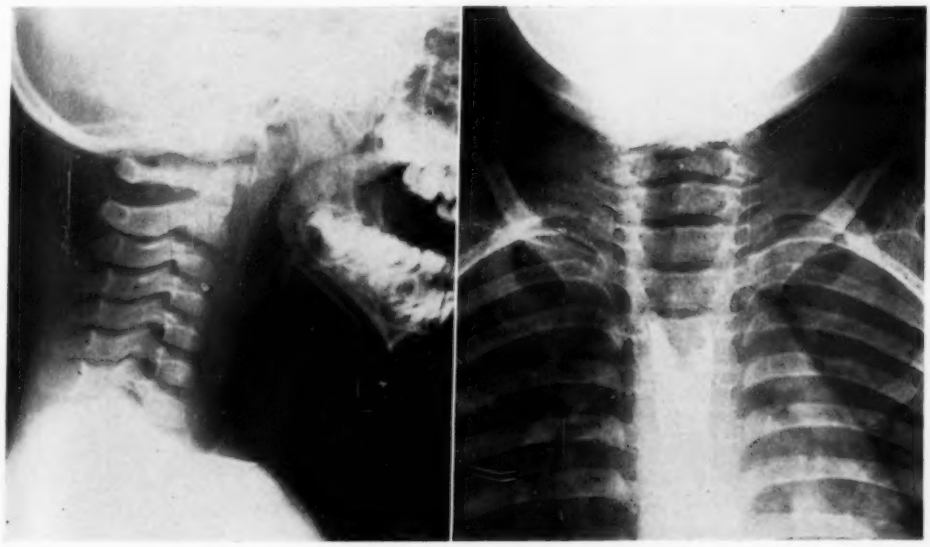
suddenly with stiffness of the neck, fever, and constipation, and was diagnosed as acute poliomyelitis. Spinal cord symptoms fluctuated markedly for more than a year before cord tumor was seriously considered, and operation performed.

Impaired function of bowel or urinary bladder was present in various degrees in twelve patients, absent in five, and not mentioned in four. This deficiency was manifested by stubborn

preciated early, but it is clear in review that urinary or bowel complaints were common in these children and might have offered material help toward determining the correct diagnosis.

SPINAL FLUID EXAMINATION

Spinal fluid examination is essential to investigation of a child whose obscure complaints or findings even remotely suggest the possibility of spinal



A. *B.*

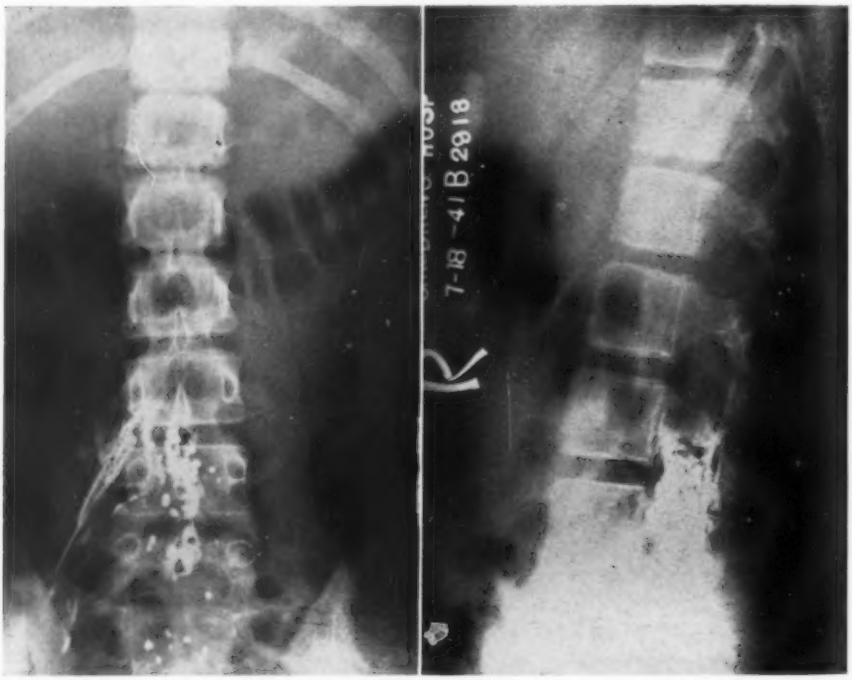
Fig. 2.—Case 8. *A*, Lateral roentgenogram of cervical spine showing loss of normal lordosis and straightening of the spine in a 2-year-old girl with a nine-month history of neck stiffness, questionable weakness of the left arm, and awkward gait. Neurological findings comprised only marked limitation in flexion and extension of the neck. Splintering of a portion of the spine with loss or increase in normal curvatures, such as shown here, is a common sign in presence of intraspinal tumor. *B*, Anteroposterior myelogram with Pantopaque, patient in steep Trendelenburg position. Plain x-rays in this projection had shown very suggestive widening of the spinal canal from C_4 to T_4, indicating probability of intraspinal tumor, and myelogram was performed to delineate lower level of the suspected mass. Operation disclosed a large intramedullary astrocytoma extending from C_4 to T_5.

constipation, urinary incontinence or retention, nocturia and frequency (probably overflow incontinence), or detected by finding relaxed anal sphincter. Significance of such symptoms was often minimized and not ap-

cord tumor.[18] Although Queckenstedt's test is likely to give an equivocal result in an uncooperative child and therefore have limited diagnostic value, the spinal fluid shows xanthochromia or increased protein content

in a high proportion of tumor cases. Spinal puncture may, therefore, prove an exceedingly valuable diagnostic agent, but it must be remembered that spinal fluid is occasionally normal even though cord tumor is present and causing complete subarachnoid block.

110 to 4,000 mg. per cent, and xanthochromia was recorded in nine, though not mentioned in others. One patient had had cisternal puncture three weeks previously which yielded clear spinal fluid with 57 mg. per cent protein and four cells per cubic millimeter, but



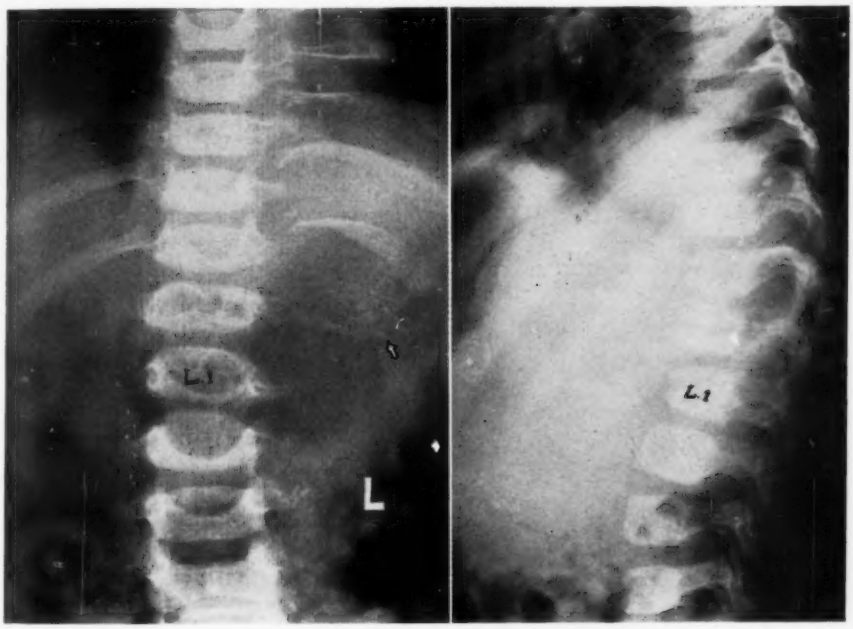
A. *B.*

Fig. 3.—Case 2. *A*, Anteroposterior roentgenogram (retouched) of lumbar spine of 12-year-old boy found to have an extramedullary ependymoma reaching from L_2 to T_8 vertebrae. Lipiodol for myelography is visible, much of the oil being in the subdural space. There is erosion of pedicles of the upper three lumbar and lower two thoracic vertebrae and widening of the spinal canal. Plain films taken one year previously show these changes clearly, but this very important evidence of tumor was then overlooked. *B*, Lateral view (retouched) with patient in inverted position, showing block at middle of L_2 vertebra. Deepening of spinal canal and enlargement of intervertebral foramina are apparent and there is nearly complete loss of the normal lumbar lordosis. Roentgenographic changes of very similar character were apparent in earlier films taken in this projection.

Nineteen of our patients had spinal puncture, and abnormalities were demonstrated in all but one who was later found to have a cystic dilatation of the filum terminale occupying the lumbar spinal theca. Spinal fluid protein was elevated in seventeen, ranging from

with repeated lumbar taps after hospital admission, no spinal fluid was secured. This discrepancy was shown later to be highly significant when an ependymoma entirely filling the lumbar spinal canal was disclosed at operation.

Queckenstedt test was considered indicative of partial or complete subarachnoid block in eight patients, not commented upon or equivocal in nine, and normal in two. One with normal Queckenstedt response had spinal fluid protein of 1,165 to 3,710 mg. per cent (three taps were done), and complete block by Pantopaque myelography. Operation revealed an intradural neurofibroma at level of the second lumbar vertebra.



A. *B.*

Fig. 4.—Case 19. *A*, Anteroposterior roentgenogram in the case of a 19-month-old boy with "hourglass" neurofibroma of lower thoracic spinal canal extending into lower chest and upper abdominal retroperitoneal space. Inner portions of the lower six ribs are eroded and left pedicles of the last five vertebrae are partially destroyed. Lacy calcification is discernible within the tumor (arrow). *B*, Lateral view demonstrating prominent kyphosis of lower thoracic spine, deepening of spinal canal in this region, and slight wedging of the twelfth thoracic vertebral body.

ROENTGENOGRAPHIC EXAMINATION

Roentgenograms of the spine demonstrate pathologic changes at the appropriate level in a high percentage of infants and children with cord tumor. These findings commonly consist of erosion of rib ends, vertebral bodies, laminae, or pedicles, and widening of the spinal canal with increase in interpedicular distance.[4] Small but significant variations may not be apparent unless searched for, and it is important that careful interpedicular measurements be made whenever spinal cord tumor is being considered.[11] It is wise to survey the entire spine unless localization is absolutely definite, because of the tendency for cervical or thoracic tumor to cause symptoms confined to the legs or other low segments for considerable intervals before as-

A.

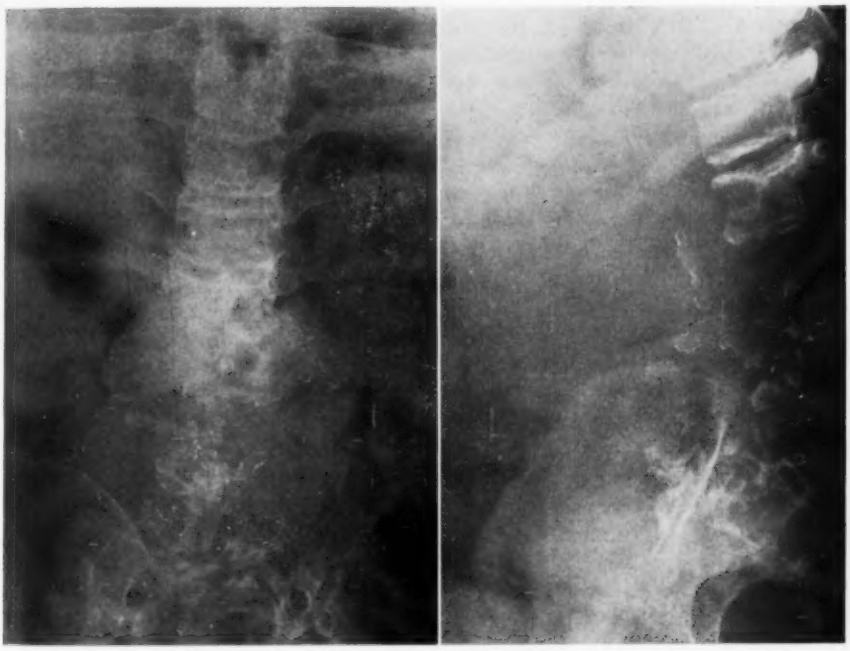
B.

C.

Fig. 5.—Case 1. *A* and *B*, Lateral and anteroposterior projections of lumbar spine of 10-year-old boy with leg pain and urinary incontinence, and later difficulty in walking. It was believed patient possibly had tuberculosis of spine or tumor of vertebra. These films show widening of upper lumbar interpedicular spaces, partial destruction of right pedicle of L_2 and L_3 deepening of upper lumbar spinal canal, and reduced lumbar lordosis. *C*, Roentgenogram of same patient twenty months later, just prior to operation. Demineralization of lumbar spine is pronounced, pedicles are destroyed, and advanced scoliosis is present. Lateral projection showed extreme deepening of spinal canal and incomplete destruction of fourth and fifth lumbar vertebral bodies. Patient had hypesthesia and considerable weakness of the lower limbs, and complete sphincter paralysis. Laminectomy disclosed a very large vascular ependymoma of the cauda equina and conus medullaris; complete removal of tumor was not possible.

cending as cord compression increases. Other roentgenographic changes associated with intraspinal tumor include kyphoscoliosis, loss of normal cervical or lumbar lordosis, striation of the vertebral body due to hemangioma, and occasionally increased density of vertebrae secondary to tumor invasion (Figs. 2 to 6).

In nine of our patients x-rays of the spine were interpreted as normal, but review of available films shows in one case pronounced pedicle thinning and separation over several segments corresponding to tumor extent (ependymoma T_8 to L_3), a finding readily apparent in films taken one year before diagnosis was established (Fig. 3, *A* and *B*). Slight widening of the neural canal at L_2 and L_3 was present, but not detected in another patient with ependymoma of the cauda equina. X-rays recorded as showing no abnormalities in three patients have been discarded, and it has not been possible to review these for possible undiscovered pathologic changes. Of ten patients reported to have roentgenographic evidence of intraspinal disease, three had been treated symptomatically elsewhere without diagnosis for several months, although x-rays taken prior to admission showed localized enlargement of spinal canal in two, and distinct erosion of sacrum in the other. Pathologic roentgenographic



A. *B.*

Fig. 6.—X-rays (retouched) of same patient shown in Fig. 5 eighteen years after operation, showing extreme destruction with nearly total loss of substance in the lower four lumbar vertebrae. Patient is now totally paraplegic but otherwise well and is able to pursue a technical occupation in radio maintenance.

findings in fourteen of our twenty-one patients may be summarized as follows: erosion of vertebral bodies and/or ribs, pedicles, 9; hemangioma of vertebra, 2; thoracolumbar scoliosis, 1; compression fracture due to sarcoma, 1; straightening of cervical spine with loss of lordosis, 1.

Myelography with Pantopaque or Lipiodol has been shown by numerous investigators to be useful for localization of tumor in questionable cases, and to resolve an occasional confusing diagnostic problem by demonstrating presence of multiple tumors, vascular anomaly, adhesive arachnoiditis, or similar unexpected lesion.[9] Lowermost extension of a space-taking intraspinal mass may be accurately delineated by this method, and when desirable, the upper pole may also be located by noting descent of a small amount of oil instilled into the cisterna magna. Myelography has particular value in a child, because the level of sensory or motor loss suspected by neurological examination may be quite inaccurate due to limited cooperation, misleading the surgeon in placement of laminectomy incision. Myelographic study should include fluoroscopic visualization up to a high cervical level in any obscure case, and is best performed with assistance of an experienced radiologist. It is not to be considered a substitute for thorough neurological appraisal, spinal fluid examination, and plain x-rays of the spine, nor should a negative myelogram be taken as absolutely excluding early intramedullary neoplasm or small tumor of the meninges.

Nine of our patients underwent myelography. In eight, complete block at the tumor level was demonstrated, and in the other a cyst of the filum terminale was sharply outlined, clarifying the previously confused diagnosis. The procedure appears to have been justified except in one patient (Case 2) whose plain x-rays revealed well-defined widening of the lumbar spinal canal at a level corresponding to clinical signs. An example of error in this method is the following experience: We recently performed myelography on a child thought probably to have a cauda equina tumor. Complete obstruction to flow of Pantopaque was clearly shown at the third lumbar vertebra, but thorough surgical exploration disclosed no mass lesion or anomaly and afforded no explanation for the apparent block.

DIAGNOSIS

History of spine stiffness and pain in neck, back, or legs, particularly at night, should make one suspicious of spinal cord tumor in a child. If in addition there is suggestion of impaired bowel or bladder control, or indications of weakness and numbness of extremities, tumor must be a first consideration. Onset may be abrupt or insidious and the course may range from a few days to many months, with variations and partial remissions.

Examination may show evidence of spinal cord dysfunction with weakness and numbness of parts below the tumor level, abnormalities of tendon reflexes, loss of superficial abdominal reflexes, and Babinski signs, depending on the segmental level of cord encroachment and relative degree of damage to the upper or lower motor neuron circuit. It is essential to recall, however, that physical findings are often meager, comprising no more than limitation of motion of the neck or back, loss (or increase) of normal

lordosis of kyphosis, and perhaps tightness of hamstring muscles.

If history and examination do not adequately clarify the diagnostic problem, x-rays of the spine should be taken and examined minutely for pathologic change. While presumptive evidence of cord tumor is often demonstrated radiologically, negative films do not of course exclude such a diagnosis, and further investigation may well be necessary. Conversely, there are several conditions simulating spinal cord tumor in which differentiation by x-ray is of great assistance: vertebral fracture or dislocation, tuberculous spondylitis, metastatic tumor, and deformities such as hemivertebra or diastematomyelia.

Lumbar puncture and analysis of spinal fluid are also of critical importance in investigation of a spinal cord tumor suspect, and usefulness of these procedures cannot be overemphasized. As mentioned in the section on Spinal Fluid Examination, there are patients with tumor in whom no abnormalities of Queckenstedt test and spinal fluid chemistry can be shown, but the great majority exhibit increased total protein, and in a high proportion the fluid is obviously xanthochromic.

Study and consideration of the patient to this point will reasonably exclude poliomyelitis, amyotonia congenita, transverse myelitis, chronic meningeal infection, and epidural spinal abscess; but for additional assistance electromyography may be very useful, particularly in distinguishing tumor from spinal muscular atrophy, infectious neuronitis, and multiple sclerosis. In the latter conditions evidence of widely scattered motor dysfunction in spinal cord and brain stem can usually be demonstrated, aiding materially in differential diagnosis.[25]

Myelography with Pantopaque or Lipiodol is indicated if simpler procedures fail to settle the diagnostic dilemma, and will reliably disclose the presence of space-taking lesion in a high proportion of persons with spinal cord tumor. This method cannot be expected to differentiate neoplasm from a large extruded intervertebral disc or an obstructive congenital intraspinal lesion, but is often exceedingly helpful in deciding the critical question of whether or not surgical intervention is demanded.

TREATMENT AND PROGNOSIS

When presence of primary intraspinal neoplasm has been established as reasonably likely, exploratory laminectomy is advisable. If sensory and motor abilities are deteriorating rapidly, operation should be undertaken as an emergency measure to achieve decompression of the spinal cord and its blood supply and thereby restrain the otherwise progressive march of cord destruction and consequent functional loss. Fulminating progression of symptoms does not by any means signify that the growth is invasive or inoperable; a benign space-taking lesion often causes such a clinical course, and operation must not be deferred solely on suspicion of hopeless malignancy.

When a circumscribed extramedullary neoplasm is encountered at surgery, it can ordinarily be removed entirely, further injury to the cord and spinal arteries being meticulously avoided. If function has not been too severely reduced by such a tumor, the result will probably be gratifying and over-all prognosis for life and neurological recovery excellent. Tumor within or densely adherent to the cord or cauda equina presents a much more

complex problem, requiring critical appraisal of the technical situation and decision as to whether the possibility of additional damage by radical removal justifies such an undertaking. Histologic examination of tumor tissue should be carried out while surgery is in progress and will often dictate how conservative or r a d i c a l operation should logically be. In dealing with an intramedullary tumor which does not present itself externally, it has often been recommended that the surgeon cautiously incise the spinal cord longitudinally at or near the dorsal midline along the presumed extent of tumor, thus providing a means for the mass to extrude itself.[10, 18] Second stage operation is performed about seven days later, at which time attack on the tumor may be considerably simplified due to improved delineation between tumor and spinal cord, if the neoplasm is of proper consistency and not unduly tenacious.

Prognosis, at least for survival, appears from the extensive follow-up data of Woltman and associates[24] to be better if ependymoma is radically removed rather than partially removed or decompressed, though with intramedullary astrocytoma little difference in long-term outlook was found by these authors, whether the tumor was removed or only biopsied. Variations in rate of tumor growth make generalizations somewhat unsafe, and there are many reports of remarkably slow recurrence of neurological symptoms following biopsy or incomplete removal of various types of glioma. This matter can be settled only by continued study and repeated examination of patients over long postoperative intervals until the end result is made clear.

In the event tumor cannot be entirely removed surgically without sacrifice of spinal cord function, radiation therapy is generally recommended. It has been difficult to determine how effectual this form of treatment is in restraining growth of gliomas because of the many variables above indicated; however, one hesitates to deny a patient the chance of benefit which radiation may conceivably offer, and there is ordinarily no specific contraindication to administration of a full therapeutic course. If tumor is of known radiosensitive type, such as neuroblastoma or hemangioendothelioma, x-ray treatment is certainly advisable, repeated if symptoms of spinal cord dysfunction recur.

Operation was performed in nineteen of our twenty-one patients, varying from biopsy to total gross removal of the lesion. Course and result in several of the group are condensed as follows: One of those not subjected to surgery was a 14-year-old girl with cyanotic congenital heart disease, as well as paraplegia and classical evidence of hemangioma of the eighth thoracic vertebral body (Case 15). She received roentgen treatment to the spine with useful improvement, but died following rupture of an intracerebral abscess about a year after discharge from the hospital. The other unoperated patient (Case 12) had an incomplete cauda equina lesion due to extradural sarcoma at the fifth lumbar level. Evidence of invasion of the vertebra was demonstrable by x-ray, causing decision against operation, and four weeks later widespread metastases were disclosed, leading to death three months after onset of illness.

Three children died within a month or less after operation. These patients

had hemangioendothelioma, malignant glioma, and widespread spinal and cranial implantation of ependymoma, respectively. Two other patients improved following surgery, but had recurrent symptoms within a few months. One with extradural round cell sarcoma died after fifteen months; the other had partial removal of an ependymoma in the thoracic cord and succumbed with paraplegia, urinary infection and decubitus ulcers four and one-half years later. In recent weeks we have operated upon four patients with spinal cord tumor and insufficient time has elapsed to permit a final statement regarding the outcome in these children. There were two with astrocytoma of the cervical cord, one extradural thoracic neuroblastoma of hourglass configuration, and one extradural sarcoma (Ewing's) invading the second lumbar vertebral body. Present status of these patients is reasonably good, with mild neurological disability, but complete removal of tumor was not possible in any, and long-term outlook is almost certainly poor.

More favorable result, at least up to the present time, has been attained in a boy aged 7 months (Case 20) who was nearly completely paraplegic at time of incomplete surgical removal of an extradural thoracolumbar neuroblastoma (primary tumor was never demonstrated). One course of radiation therapy (3,000 r) was given and disability steadily lessened. Currently, six and one-half years later, there is pronounced kyphoscoliosis and mild tendency to urinary incontinence, but no impairment in function of the legs. Radiation also appeared effective in a patient (Case 14) with extradural hemangioma at T_6, associated with hemangiomatous striation of the vertebral body and numbness with mild spastic weakness of the lower limbs. The tumor was partially removed and 3,000 r therapy administered, with improvement. Now fourteen years later, patient shows no neurological findings and is completely free of symptoms.

Opposed to this is the record of a partially paraplegic child (Case 1) with extensive ependymoma of the lower thoracic spinal cord and filum terminale, who had incomplete removal of the tumor plus minimal radiation therapy with only transitory improvement. Examination eighteen years later (1952) revealed total paraplegia and a large firm mass protruding in the lumbar area; x-rays demonstrated remarkable distortion and erosion of the spine (Fig. 6). Another child (Case 2) with extramedullary ependymoma extending from T_8 to L_5 had subtotal removal of tumor and a total of 3,000 r radiation. When last seen, nine years later, there were still no signs of recurrent paraparesis and patient was entirely free of symptoms.

Neurofibroma was present in three cases, the tumor arising from a cauda equina root in two instances and forming a dumbbell mass with intra-abdominal extension in the other. Complete extirpation of tumor in the first two patients resulted in apparent cure with negligible residual (fifteen- and seventeen-year follow-up), whereas the other child became increasingly paraplegic after incomplete removal of tumor although he has survived eight years.

Results in our patients may be summarized thus: The outcome was unsatisfactory with early death or recurrent disability known to be present in

ten, and very probable in at least two others (recent cases). Result is unsettled but probably will be poor in six additional patients whose present status is good, because tumor regrowth is almost certainly to be expected. In only five patients can the outcome be classed as satisfactory with insignificant neurological disability and no reasonable chance of tumor recurrence. This group includes the patient with cystic lesion of the cauda equina (Case 6) in whom postoperative interval is too short to allow absolute conclusions, though probability is strongly in favor of cure.

In spite of the disheartening results in so many of our patients, one may fairly conclude that a reasonable number were benefited by treatment, and given months or years of relatively normal existence before continuing tumor growth finally overwhelmed the spinal cord. For therapy to yield even temporary improvement, however, it is essential that the tumor be removed or spinal cord decompression effected before function has been hopelessly compromised. Spinal cord destruction with inevitable paraplegia, paralysis of sphincters, urinary tract infections, bed sores, and permanent invalidism results as readily from benign as from malignant tumors, and only early diagnosis and well-directed treatment can save those patients with a curable lesion from this unfortunate fate.

CONCLUSIONS

1. Twenty-one children with intraspinal neoplasm are reported, and clinical and pathological features of these patients are elaborated together with therapeutic methods and final results. Diagnostic importance of roentgenologic and spinal fluid examinations is emphasized.

2. Reports of previous writers are reviewed and the general subject of spinal cord tumor in infancy and childhood is discussed with respect to pathology, diagnosis, treatment, prognosis, and other significant aspects.

3. It is again stressed that a patient who has a spinal cord tumor may often exhibit only stiffness and pain on motion of the spine at the approximate level of tumor for many months before sensory, motor, or reflex abnormalities are detectable.

4. Although percentage of surgically favorable cord tumors in children is small, awareness of the possibility that tumor may be present is highly essential to permit cure whenever possible and preclude total permanent neurological loss.

We are indebted to Dr. Wilbur Thomas, Staff Pathologist, for his very helpful assistance in reviewing and classifying the pathological material on these patients.

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ADDENDUM

Since submitting this paper for publication, we have treated another child with spinal cord tumor, bringing our case total to twenty-two. This patient was a 12-month-old girl who developed weakness of the right arm and stiffness of the neck after a fall one week before admission. Left arm also became paretic, and tendon reflexes disappeared in both upper limbs. Cervical x-rays showed loss of lordosis, spinal fluid protein was 234 mg. per cent, and myelography disclosed complete block at C_6. Intramedullary astrocytoma grade II was exposed by cervical laminectomy and dorsal myelotomy from C_2 to C_5, and partial removal was accomplished. Weakness of the arms has lessened notably, and early convalescence is satisfactory.

MECONIUM ILEUS (COMPLETE OBSTRUCTION) IN A PREMATURE INFANT

Medical and Surgical Treatment With Recovery

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In 1905 Landsteiner[1] first described the association of fibrocystic disease with meconium ileus. Hurwitt and Arnheim[2] substantiated his findings in 1942. Farber[3] furthered this work with some eighty cases at autopsy and published his findings in 1944. Since then Hiatt and Wilson[4] have reported eight cases in which four patients survived. The relationship is further mentioned and elaborated upon in Brennemann's *Practice of Pediatrics*.[5, 6] A review of the literature does not reveal a case in a premature infant prior to this report.

CASE REPORT

History.—A three-week premature infant, weighing 4 pounds 11 ounces, delivered spontaneously, followed by routine tracheal catheter resuscitation. The first symptoms were noted on the third day of life, at which time there was slight distention of the abdomen and the patient did not desire food. An enema was administered, and the solution returned clear except for three large mucus plugs. A hypodermoclysis of 55 c.c. lactate-Ringer's solution was given, and crystalline penicillin was started in a dosage of 20,000 units every three hours, intramuscularly. The following morning the infant was vomiting after each feeding and the abdominal distention had become more marked. The weight had dropped to 4 pounds 3 ounces.

Physical Examination.—The examination revealed a premature infant appearing slightly dehydrated and very slightly cyanotic. There was a slight expiratory grunt clearly audible. The physical examination was entirely negative except for the findings in the abdomen. The abdomen was moderately distended with visible intestinal patterns. It was generally soft though tympanitic. Peristaltic rushes could be heard on auscultation. An anus was present and admitted the tip of the examining finger. The rectum contained no fecal matter.

X-ray Findings.—An anteroposterior roentgenogram of the abdomen revealed gaseous distention of the small bowel, confirmed by barium enema. The ileum was markedly distended and there was evidence of a finely granular type of density close to the right border of the abdomen and appearing to lie in the ileum. The distention funneled down to this density. These findings strongly suggested an intestinal obstruction due to a meconium plug.

Anteroposterior roentgenogram of the chest was reported as essentially negative.

Operation.—The patient was operated upon, after a cut-down on the medial malleolar vein was done, and a polyethylene catheter inserted. A transfusion was started and, under local anethesia, a right rectus midabdominal incision was made. On entering the peritoneal cavity a widely dilated jejunum and ileum were found funneling down to the ileocecal valve. There was no malrotation present and no evidence of congenital atresias. The colon appeared embryonic and was no larger than a lead pencil. It did not contain any meconium. The most distal ileum contained hard, inspissated meconium, and the ileocecal lumen was not patent. A Wangensteen aseptic decompression was performed in the following manner: A purse-string suture was placed in the

ileum and drawn moderately snug. An ileotomy was then performed and an attempt was made to suction out the inspissated meconium. This was unsuccessful because of the sticky consistency, and it was then necessary to instill 10 per cent pancreatic solution, which had been prepared for this contingency, and then suction instituted. This proved successful and large amounts of meconium were removed. Some meconium near the ileocecal valve was manually milked toward the ileotomy opening. Because all of the meconium could not be removed, some of the pancreatin was left in the intestinal tract and the ileotomy wound closed. The abdomen was then closed in layers without drainage.

Following operation, negative suction was immediately instituted and the baby was placed in an incubator with constant oxygen therapy. Proper electrolyte balance and antibiotic therapy were carefully maintained, a second transfusion given, and on the second postoperative day water with dextrose was started as feedings. The baby retained all fluids by mouth and 1 grain of pancreatin was added to each feeding. The following day frequent weak protein milk feedings were started. The child began to retain all food, and after thirty-six hours she began having normal-colored stools. Each day progress was good and the child remained hospitalized until she weighed 5 pounds. An analysis of the

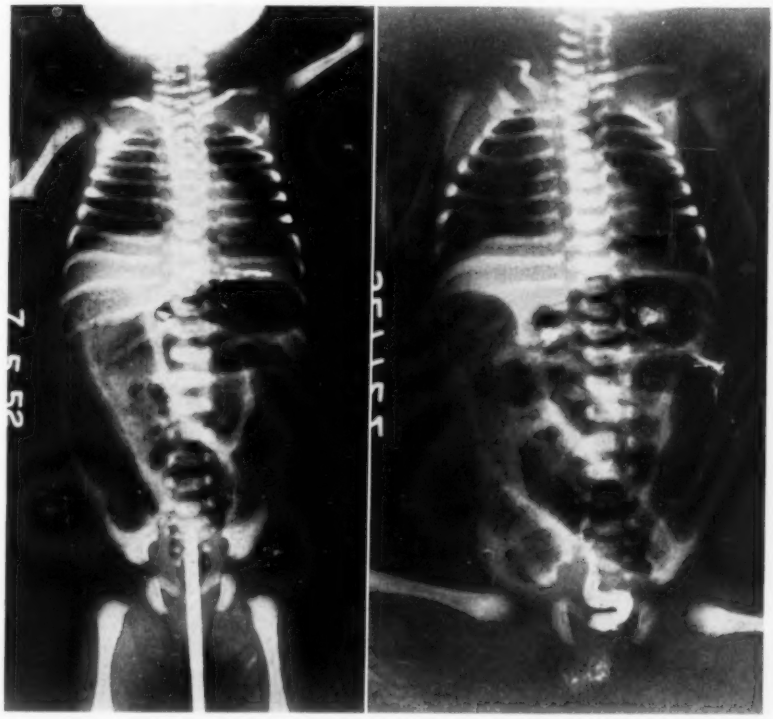

Fig. 1. Fig. 2.

Fig. 1.—Abdominal scout film revealing marked gaseous distention of small bowel.
Fig. 2.—Barium enema showing colon outlined with absence of distention. Note tremendous small bowel distention as compared with colon.

duodenal contents two weeks following operation revealed only a trace of trypsin. A test likewise on the stool revealed the same results. These tests revealed similar results at the age of 4 months. This confirmed the diagnosis of cystic fibrosis of the pancreas. At the age of 4 months the weight had risen to 10 pounds 4 ounces. General development has been excellent.

Fig. 3.—Infant at 4 months of age.

Since dismissal from the hospital, the patient has been kept on a regime best suited to the pancreatic deficiency. The best formula in her particular case proved to be a skimmed milk base with sufficient Alacta added to meet caloric requirements. Apple, banana, strained meats, and unflavored gelatin have been added to the diet. She has received a multiple vitamin and a hematinic preparation.

Pancreatin added to the feeding did not seem to be of any value. She has received a biweekly injection of Bicillin, as oral antibiotics seemed to increase the frequency of her stools.

Although her growth and nutrition have been excellent, she has had febrile episodes every ten to fourteen days, lasting two days or less. At these times there have been no other symptoms, examinations have been negative, and x-rays of the chest normal. We have found them to subside spontaneously without the addition of other antibiotics, and our only treatment of the last three episodes has consisted of acetylsalicylic acid.

DISCUSSION

This case typifies the close cooperation that must be present between pediatrician and surgeon. Care of such an infant requires both medical and surgical care. Complete intestinal obstruction from whatever cause requires surgical intervention and in these cases requires the removal of the inspissated meconium as soon as the diagnosis is made. The actual point of obstruction is at the ileocecal valve, the meconium being so thick that it cannot pass into the large bowel. This produces increasing distention of the small bowel and eventually perforation and generalized peritonitis unless surgical relief is obtained.

The simplest and most expedient mechanical relief may be obtained by a Wangensteen decompression procedure. An extremely valuable adjunct is the use of pancreatin solution as an irrigating solution to remove the sticky viscid meconium.

Once the obstruction is relieved and the child is having bowel movements, the medical management becomes all-important. Proper attention to diet and to the control of intercurrent in-

fections is of prime importance. These children in the past have not reached maturity, most often because they expire from some intercurrent infection such as bronchiolitis, pneumonia, upper respiratory infection, otitis, etc. They are particularly susceptible because of the lack of vitamin A in the system. Diets consist of high protein, low fat and starch, and hematinics. Intolerance to fat with production of steatorrhea is well known.

Numerous references may be found in current literature concerning the management of the pancreatic fibrosis.[7, 8, 9] Suffice to say, the main object of treatment is maintenance of a positive nitrogen balance, with growth and development approximating normal. This may be accomplished with proper diet and supplements, despite the persistence of a moderate increase in frequency of stools, as is readily seen in this particular case.

To date there has been no definite evidence in this case of the fibrocystic disease of the lungs which usually accompanies cystic fibrosis of the pancreas.

SUMMARY

This is a case of a three-week premature infant with acute intestinal obstruction due to meconium ileus with pancreatic fibrosis being the underlying etiology. Therapy consisted of early diagnosis, early operation, and proper postoperative care. Unusual interest must be maintained in these cases until and after adulthood is reached.

ADDENUM

In a current publication by Gross and Ferguson,[10] from the Children's Hospital and Harvard Medical School, spanning the years 1936 through 1951, 159 operations were performed for various congenital anomalies in premature infants. There were no survivals in six cases operated upon for meconium ileus.

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OSTEOCHONDROMA OF THE DISTAL FEMORAL EPIPHYSIS

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ON FEB. 11, 1952, we examined a patient with an atypical osteochondroma involving the medial femoral condyle which was gradually producing a genu valgum deformity (Fig. 1, *C*). Review of the literature does not reveal a case report exhibiting similar findings or reference to the existence of such a condition. The osteochondroma was contained entirely within the medial femoral condyle. Except for a generalized enlargement of the condyle, it did not produce any external evidence of tumor formation. Typical osteochondromas or exostoses project as tumor masses from the host site. Dr. John Caffey at the Babies Hospital in New York has films of a similar case which has not been reported.[1]

CASE REPORT

S. M. (Unit No. Q-1045), a white girl, 9 months old, was referred to the Children's Hospital, Pittsburgh, because of increasing valgus deformity of the right knee. Although the development of the deformity was gradual, the mother stated that it had increased rapidly during the three weeks preceding admission. There was no history of injury, pain, or fever. The child is a twin (one egg). The cotwin appears normal. She has had no x-ray examination. The mother's pregnancy, and the growth and development of the child to date, had otherwise been normal, and there was no familial history of a similar deformity. The vitamin intake and diet had been adequate.

The positive findings on physical examination were limited to the right knee. There was a flexion deformity of 40 degrees with a 30 degree genu valgum. The knee flexed completely, but could not be extended beyond 140 degrees. There was no synovial thickening or increase in synovial fluid. The circumference of the right knee was 18 cm. as compared with 16½ cm. for the uninvolved right knee.

Admission roentgenograms (Fig. 1, *A*, *B*, *C*) showed numerous clusters of shadows of calcium density located just medial and distal to the ossified portion of the distal femoral epiphysis. Roentgenograms of the remainder of the skeleton were normal. A pneumoarthrogram was done (Fig. 2). This outlined the distal end of the right femur and demonstrated that the calcium densities lay within the cartilaginous distal femoral epiphysis. The medial femoral condyle was larger than the lateral condyle.

Routine laboratory studies, including urinalysis, complete blood count, Kahn test, tuberculin, nonprotein nitrogen, calcium, phosphorus, and alkaline phosphatase, were all within normal limits. The erythrocyte sedimentation rate (Wintrobe) was twenty-one. Elevation of the sedimentation rate persisted, and two months later it was 36 mm. in one hour. We are unable to explain this finding.

On Feb. 18, 1952, arthrotomy of the right knee was performed. At operation the medial femoral condyle was enlarged. The articular surface appeared normal, except for the presence of bluish-gray areas of discoloration, which were spotted over the articular surface of the medial femoral condyle and appeared to be deep to the articular surface. The medial

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A. *B.*

C.

Fig. 1.—*A*, Admission x-ray showing tumor mass. *B*, Admission x-ray (lateral view) showing tumor mass. *C*, Admission x-ray showing valgus deformity.

condyle was partially excised and trimmed so that its contour was approximately normal in size; when this was done the valgus deformity could be corrected. In the course of removing the articular cartilage and part of the cartilaginous portion of the epiphysis, the tumor tissue was reached at a depth of 6 mm. It was gritty in spots and had the typical appearance of osteochondromatous tissue with predominance of the cartilaginous elements.

The postoperative convalescence was uneventful. The return of motion in the knee joint has been slow. Roentgenograms taken postoperatively demonstrate that the lesion had been incompletely removed (Fig. 4). It will be followed with serial films. The leg is being held in a three-point pressure brace to help prevent a return of the valgus and flexion deformity.

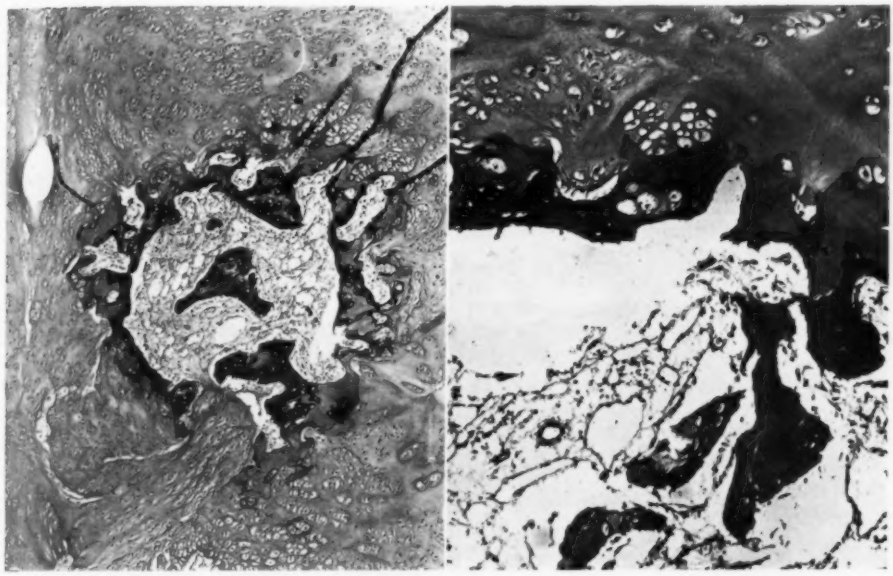
The material removed from the medial condyle was examined by Dr. George Fetterman, pathologist at the Children's Hospital. The following is his report: *Gross:* The gross specimen consisted of many fragments of firm, pearly-white tissue from the medial condyle of the right femur. The tissue, principally cartilage, was firm and presented a peculiarly fine, lobulated, hard, shiny, cut surface. The cut surface of these shavings presented many opaque whitish spots averaging 2 mm., interspersed with tiny pin-point pitted areas. Here and there were brownish areas of ossification. *Microscopic:* Sections, all of which were made transversely, revealed lobulated, actively growing hyaline cartilage, containing many islands of new bone (Fig. 3, *A*, *B*, *C*). The growth appears histologically benign. *Diagnosis:* Osteochondroma.

A. *B.*

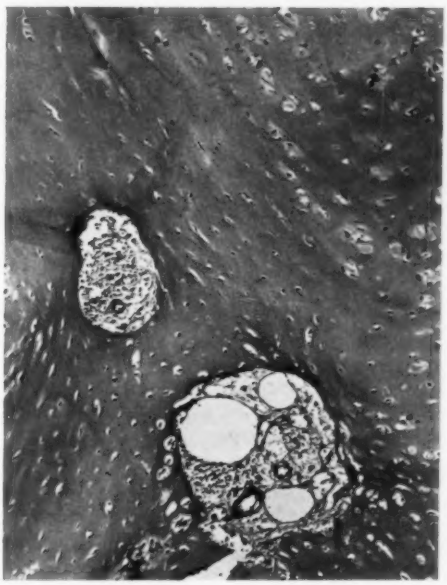
Fig. 2.—*A*, Pneumoarthrogram (anteroposterior view) showing tumor confined within condyle. *B*, Pneumoarthrogram (lateral view) showing tumor confined within condyle.

DISCUSSION

It is evident from the appearance of the condyle after partial excision and from the residual shadows in the x-ray pictures (Fig. 4) that the tumor mass has been incompletely removed. At the time of operation, it was not possible to remove the tumor mass, leave the articular cartilage untouched and still correct the deformity. It is anticipated that this child will develop a new articular cartilage, which may be more fibrous than hyaline. Specu-



A. *B.*



C.

Fig. 3.—Photomicrograph of sections of tumor. *A*, Showing representative focus of bone formation. Enclosed in the bony structure is fatty marrow. Surrounding is hyaline cartilage. (×40, reduced 2/7.) *B*, Showing greater detail in area similar to that in *A*. (×140, reduced 2/7.) *C*. Showing a purely cartilaginous portion of tumor. (×140, reduced 2/7.)

lation concerning the course had the tumor mass been left untouched is interesting:

1. Would the condyle have continued to increase in size indefinitely with increasing valgus deformity?

2. What would have happened to the tumor mass when the ossification of the cartilaginous portion of the epiphysis had extended so as to involve the tumor?

A. *B.*

Fig. 4.—*A*, X-rays (anteroposterior view) taken postoperatively, demonstrating that the lesion had been incompletely removed. *B*, X-ray (right lateral view) showing same as *A*.

3. Would the ossification of the epiphysis as a normal growth procedure have invaded the tumor and replaced it with normal bone structure leaving the child with the residual valgus at the time of this invasion, or would the tumor mass have remained an isolated portion of the condyle?

Some of the answers to these questions may develop as the growth of the medial femoral condyle and the residual tumor mass are followed with x-ray films.

This condition may be one of the unrecognized causes for the development of unilateral bowleg or knock-knee.

CONCLUSION

A case of osteochondroma of the medial femoral condyle contained entirely within the cartilaginous portion of the distal femoral epiphysis is presented. This produced a flexion and valgus deformity of the knee. To our knowledge, only one other similar case has been observed.

The authors' acknowledge the aid and advice of Dr. George Fetterman, Pathologist of Children's Hospital, Pittsburgh, Pa.

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Psychologic Aspects of Pediatrics

THE EARLY DEVELOPMENT OF CHILDREN WITH SCHIZOPHRENIA

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CHILDHOOD schizophrenia is being recognized with increasing frequency. Though the condition is not as common as in adults it is by no means rare and it should be considered in the differential diagnosis of every child with a severe behavior disorder.

Views as to the genesis of childhood schizophrenia differ. Kanner[1] regards these children as reacting to cold, indifferent, undemonstrative parents. Unable to set up satisfactory relationships with his parents or substitutes, the child withdraws. According to psychoanalytic interpretation,[2] the principal difficulty centers about "narcissistic regressions or fixation with difficulty in ego and superego development." Geleerd[3] considers the schizophrenic process to arise from the child's difficulty in setting up an adequate image of his mother that he can deal with in her absence.

Bender and Freedman[4] regard these, not as explaining how the schizophrenia arose, but rather as descriptions of what is going on in the mind of the sick child. They look upon childhood schizophrenia as an encephalopathy.[5] To support this view they point to the familial nature of the condition as shown by the high incidence of psychoses in other members of the family. Their thesis is further borne out by studies on twins[6] which indicate that heredity is a prominent etiological factor. The incidence of schizophrenia in the one-egg cotwins of afflicted children is about 68 per cent, whereas in two-egg twinships the cotwin is affected in only 15 per cent of the cases. The fact that in one-egg cotwinships the cotwin was free of the disease in 32 per cent of the cases indicates that environmental factors play a not inconsiderable role.

To further support their viewpoint, Bender and Freedman analyzed the early developmental histories of eight children in whom a diagnosis of schizophrenia had been made before the age of 5 years. Seven of these were their own cases; one had been described earlier by Tramer.[7] The data were obtained from diaries and baby books kept by the mothers and were compared with the behavioral norms of Gesell.

All eight children were born at term or after term; one was delivered by cesarean section. The weights at birth varied from 6 pounds 1 ounce (2.8 kilograms) to 9½ pounds (4.3 kilograms). Among the notations made by mothers at birth were: "looked

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premature"; "looked like a thin, little old man"; "extraordinarily pale; delicate and beautiful"; "had no fight in him"; "looked like a sober, disapproving, little old lady."

Most of the babies did poorly during early infancy, requiring frequent changes of formula. There were complaints of diarrhea, vomiting, colic, pylorospasm, excessive crying, and poor sleep. Gastrointestinal upsets and respiratory infections were frequent. Somewhat later, difficulties were encountered in introducing solid foods. Irregularities in motor development were also observed. Two children showed precocious activity, being able to crawl at 4 weeks; later they both lapsed into practical immobility for months.

At 4 months, most of the mothers noted frequent respiratory infections, the babies appearing excessively ill with all infections. Gastrointestinal symptoms and gagging were also common.

At 6 months the children appeared unhappy. Rhythmic habits were often indulged in to excess. Sleep was restless. Frequent colds and gastrointestinal symptoms, such as constipation, diarrhea, gagging on food, foul breath, continued. Emotional instability, as evidenced by intense interest in an object alternating with apathy, outbursts of rage, excessive shyness and screaming at the approach of strangers appeared at this time. Several of the mothers remarked on the babies being unusually beautiful and made the point that they had an ethereal, particularly translucent kind of beauty which was different from that of the normal baby.

At 12 months, the preschizophrenic children were reported to be overly susceptible to respiratory infections, often with high temperatures and marked sweating. Some were large, obese and flabby, others tall, pale and asthenic. Motor activity varied widely. Some babies were lethargic, others overactive. As a group they were considered by their mothers to be extraordinarily shy and dependent. A lack of responsiveness and of ability to vocalize was observed in some children. At one time or another four of the eight children were considered to be deaf, though they were not.

By 2 years the preschizophrenic children manifested many of the features characteristic of their disease. They displayed many fears—of high ceilings, strange places, rapid movements as in trains or elevators. Ritualistic or compulsive behavior was prominent. Despite their dependency and demanding behavior, the youngsters did not respond in normal fashion to affection and were often referred to by their mothers as "remote." Some avoided other children or were openly hostile.

At 2½ years, regressive behavior was already present, particularly in speech. One child, who formerly showed a precocious interest in nursery rhymes and books, lost these interests and became compulsively preoccupied with kitchen drawers, pots, electric plugs. Another youngster, previously able to repeat a nursery rhyme in Italian, lost this ability and ceased talking entirely. Play at this age was compulsive and destructive. Violent temper tantrums were also seen.

The observations of Bender and Freedman are open to two criticisms: the lack of a review of the diaries and baby books of a comparable group of normal children, and the fact that the

diaries and baby books in the schizophrenic children were kept by mothers who are themselves suspect of unusual behavior, and whose descriptions and interpretations of their children's behavior must therefore be accepted with reservations.

Nevertheless the data suggest that schizophrenia, even in young children, may be foreshadowed by unusual behavior for several years before the disease becomes manifest and may even be present at birth. Further evidence that childhood schizophrenia may be present during the early months of life has been presented by Bergman and Escalona.[8] They described a group of children who as infants showed unusual sensitivity to sensory stimuli—sound, touch, temperature, equilibrium, light, color, taste, smell, and so on. One baby 10 months of age reacted violently to color. She almost leaped out of her mother's arms when she saw a bouquet of red flowers, and she refused to eat foods which were yellow. Later on, she reversed herself and all her clothes had to be yellow, never red. The children showed precocity in certain aspects of their personalities and gave the impression of being unusually gifted. On further observation and closer study, however, it was found that most, if not all, of these children developed childhood psychosis.

In summary, then, the viewpoint of Bender that childhood schizophrenia is an encephalopathy is supported by (1) the familial nature of the illness, (2) the data from studies of the disease incidence in twins, (3) the observations of Bergman and Escalona, and (4) the developmental studies of Bender and Freedman.

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Clinical Conference

CLINICAL CONFERENCE, ST. LOUIS CHILDREN'S HOSPITAL
A CASE OF TETANUS

PREPARED BY HULDA J. WOHLTMANN, M.D., RESIDENT

DR. HULDA J. WOHLTMANN (Resident).—J. S., an 11-year-old white girl, was admitted Oct. 22, 1952, because of rigidity of the muscles of her back and neck, and difficulty in breathing. She had injured her left leg on a barnyard post ten days prior to her admission. The wound was left untreated for two days, but because of pain, swelling, and a purulent discharge, she was taken to her family physician who gave her an injection of penicillin. Eight days following the injury she complained of neck and back pain, and on the ninth day she was taken back to her family physician who found that she could not open her mouth widely and prescribed a gargle and some pills. The following day she was seen again by her physician because of considerable pain, difficulty in breathing, and inability to open her mouth. The diagnosis of tetanus was made, and she was given 3,000 units of tetanus antitoxin and referred to this hospital.

Physical examination revealed a well-developed and well-nourished child who preferred to lie in a prone position because that was the only way she could breathe. Her blood pressure was 120/70, pulse 120 per minute, and her rectal temperature was 38.2° C. Trismus was present. Her neck was arched, and she complained of pain over the lower thoracic vertebrae. The abdomen was flat, but the abdominal muscles were quite rigid. There was a small, clean, open lesion on the anterior aspect of the lower third of the left leg.

She was sedated with rectal Avertin (80 mg. per kilogram). This was given at intervals when opisthotonos and convulsions occurred. Various intravenous fluids were started through a cutdown, such as 5 per cent glucose in water; lactate-Ringer's; Ringer's; dextrose-Amigen-lactate-Ringer's; serum albumin; and blood. A tracheotomy was performed, and she was placed on penicillin prophylactically. She was given 50,000 units of tetanus antitoxin intravenously and 50,000 units intramuscularly.

On October 26, she was noted to be slightly cyanotic, but when placed in oxygen her color improved. During her first week of hospitalization, her temperature fluctuated between 38° and 40° C. She was placed on streptomycin, terramycin, and penicillin.

On October 28, her breathing was difficult, and aeration of the left lower lobe was poor. Her tracheotomy tube was changed with only slight improvement. During the afternoon, she began having tonic seizures. Rectal Avertin was given and shortly thereafter expelled. The dose was repeated in ten minutes, and two to three minutes later respirations ceased. A

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breathing bag was attached to the tracheotomy tube, and artificial respiration was given. Later she was transferred to a tank respirator. Sedation then was attempted with Demerol but was unsatisfactory, and Avertin anesthesia was resumed.

On October 30, a low bronchoscopy was done. Several crusts of moderate size were noted in the region of the carina and in the main bronchi. Rather copious and somewhat thick secretions were noted which were adherent to the bronchial walls. There were small areas of ulceration in the right main bronchus and trachea. Aeration improved following bronchoscopy.

Intravenous Sodium Pentothal was substituted for Avertin on October 30 and given intermittently when needed for sedation for a three-day period.

While the patient was in the respirator, it was frequently necessary to assist respirations by attaching a breathing bag to the tracheotomy tube when respirations were ineffectual.

On November 2, the patient's color was good, and it was noted that she was breathing spontaneously about twice as rapidly as the respirator. Later that day she maintained a good color with the respirator turned off, even though her respirations were gasping in type. There were both fine and moist râles throughout both lung fields. The heart tones were of fair quality, and no murmurs were heard, but a gallop was present. Her liver could be palpated three fingerbreadths below the right costal margin. She was generally edematous, and her urinary output was poor. Digitalis was begun, and she improved slowly.

Because of absent breath sounds over the left lower lobe, she was again bronchoscoped on November 4, and a moderate-sized crust was removed from the left main stem bronchus. The mucosa of the left bronchus was very red and edematous.

During her second week of hospitalization, her temperature fluctuated between 37° C. and 40.7° C. Polymyxin was given for three days, and intravenous triple sulfonamides were given on November 4 and 5.

Because she was still edematous, all intravenous medications and fluids were discontinued on November 5. The following day intravenous terramycin was restarted because her temperature rose to 40° C. Later that day the swallowing reflex was noted to be present, and she was started on small oral feedings consisting of a mixture of equal parts of dextrose-Amigen-and a special salt solution. She moved her arms and legs, but did not respond when her name was called. On November 7, urticarial wheals and wheezing respirations were noted which responded to Adrenalin. Deep tendon reflexes were hyperactive, and there was bilateral sustained ankle clonus.

Tube feedings were begun on November 8. Two days later, she recognized her mother and cried whenever she was given shots. This was nine days after Sodium Pentothal had been discontinued and nineteen days after admission.

During her third week of hospitalization, her temperature ranged between 37.5° and 39.9° C. She was on penicillin and terramycin. She had several tarry stools during this week. She was able to move her legs but could barely move her hands and did not move her arms.

TABLE I

DATE	NPN MG.%	pH, SERUM	HCO_3^- MEQ./L.	NA MEQ./L.	K MEQ./L.	CL MEQ./L.	TOTAL PROTEIN GM.%	ALB. GM.%	GLOB. GM.%	CA MG.%	PHOS. MG.%	HB. GM.%	RBC (MILLION/CU. MM.)	WBC/CU. MM.
10-24	20.0		24.4	137.2	3.5	104.8						13.4	4.95	20,000
10-27							5.36	3.74	1.62					
10-29		7.4	42.0			89.4								16,450
11-2	62.0		48.7			78.0								
11-4	71.5	7.42	45.4	142.2	4.4	80.0	4.28	2.41	1.87	8.9	4.4	10.8	3.42	17,200
11-10	57.5		43.6			99.0	4.48	2.66	1.82			8.0		14,050
11-13	44.5		32.4	137.2	3.5	100.0	5.1	2.9	2.21					
11-20	44.0		29.7									11.3		18,750
12-9	34.5											12.3	4.47	9,120
12-3	EEG—a definite slow dysrhythmia consistent with diffuse organic basis for complaints.													

During her fourth week of hospitalization, her lung fields cleared except for decreased breath sounds at the right apex. There seemed to be some memory loss. The upper extremities appeared to be weak, but function seemed to be returning, and physiotherapy was started. Her temperature varied between 37.2° and 38.4° C. All antibiotics were discontinued except penicillin.

She was gradually taken off all medications except vitamins. A decubitus ulcer of the left lateral malleolus slowly healed. She regained the function of her arms, began to walk, and her memory improved. She continued to have atelectasis of the right upper lobe which was clearing by x-ray at the time of her discharge on December 12. (Table I.)

DR. ALEXIS F. HARTMANN.—It was difficult to keep this patient's muscles relaxed enough to permit adequate respiration. When the amount of anesthetic was increased enough to overcome tetanus, spontaneous respirations ceased. Rectal Avertin was the first anesthetic used, but it was not completely satisfactory. Twice some of the dose was expelled, and a second make-up dose proved excessive. Absorption apparently sometimes is very rapid. Proctitis may develop from repeated use of rectal Avertin. Dr. Moyer suggested using intravenous Sodium Pentothal. Anesthesia could be obtained quickly with this drug, but the effects seemed to last too long. Our patient remained unconscious for a period of nine days following the last dose of Pentothal. The question was then raised whether this was due to the Pentothal or to some central nervous system effect of the tetanus. Dr. Eastwood, would you comment on the choice of anesthetic in tetanus?

DR. DOUGLAS W. EASTWOOD (Assistant Professor of Anesthesiology).—The rectal route of administration of Avertin is objectionable because of irregular absorption, slow onset, and proctitis. Pentothal or 1 per cent Avertin can be given intravenously.

EOS.	JUV.	STAB.	SEG.	LYM.	MONO.	PLATELETS	C.C. FLOCC. TEST 24 HR.	C.C. FLOCC. TEST 48 HR.	pH, URINE	ALBUMINURIA	GLYCOSURIA	SPECIFIC GRAVITY	MICROSCOPIC
2		20	57	17	4	adeq.			6.0	tr.	0	1.008	Few granular casts.
3	6	18	59	11	3	adeq.			6.0	0	0		35-75 WBC/hpf, 30-50 RBC/hpf.
	3	14	68	10	5	adeq.							
2		21	50	24	3	adeq.			7.5	tr.	0	1.025	0-3 WBC, rare RBC, and hyaline cast.
							3+	4+					
		6	78	11	5		2+	2+					
2			40	52	6	adeq.			5.5	0	0	1.025	2-4 WBC with occasional RBC.

However, intravenous Avertin usually causes a thrombophlebitis. The duration of action of intravenous Avertin is comparable to Pentothal after a level of narcosis has been established. Repeated doses will depress the patient. Both have cumulative effects. Following the use of Pentothal, a patient may sleep twenty-four hours. Richards has shown that Pentothal is distributed throughout the total body water.

Dr. Carl A. Moyer (Professor of Surgery).—Absorption from the rectum is uncontrollable. In Michigan, the results of treating tetanus with Avertin as the anesthetic were practically no better than the results obtained in Europe during the 1700's. Recently, in Dallas, intravenous Sodium Pentothal was substituted for Avertin. After the first and second days the amount of Pentothal required was very small, and the incidence of convulsive seizures was practically nonexistent. The level of anesthesia could be kept light, and patients could often talk and swallow. In thirteen cases of tetanus in Dallas, using Pentothal, one death resulted. The depth of anesthesia should be no greater than that necessary to prevent convulsions.

Dr. Hartmann.—Dr. O'Leary, you have suggested the use of intravenous Benadryl as a muscle relaxant.

Dr. James L. O'Leary (Professor of Neurology).—Intravenous Benadryl may be of use in muscle spasm. In the treatment of Parkinsonian patients with antihistamines, it was found that they could tolerate large doses of that drug, and muscle relaxation was sometimes striking. Excessive and prolonged use in this instance, however, might depress respiration.

Dr. Hartmann.—The choice of an anesthetic is still an open one. Even though most of our experiences with Avertin have been satisfactory, we probably should start treatment of a patient with Pentothal for comparison. Dr. O'Leary, didn't we once

have a case in which Benadryl was thought to cause convulsions?

DR. O'LEARY.—I do not remember. Antihistamines probably do aggravate a dysrhythmic pattern.

DR. HARTMANN.—Another question—Should we perform a tracheotomy routinely? Convulsions are often associated with laryngospasm. If a tetanic convulsion occurs with cessation of respiration and a tracheotomy has already been done, one can effect pulmonary exchange of oxygen and carbon dioxide with the use of the breathing bag. Secretions or any aspirated material can be suctioned through a tracheotomy. If secretions inspissate, this material can be thinned out or moistened and suctioned out by the use of a bronchoscope. But there are objections to tracheotomy. The amount of secretions will increase. The tube may be too long or too short, too curved, or too straight, and it has to be kept clear of secretions. When this child was tilted to one side, one often could not hear any breath sounds on the side which was down. Dr. Ogura, would you comment generally on the problem of tracheotomy in tetanus?

DR. JOSEPH OGURA (Associate Professor of Otolaryngology).—In 1837, Curling first recommended the use of tracheotomy in tetanus. In 1857, Humphreys in England tracheotomized tetanus patients. Galloway in 1949 suggested that patients with bulbar polio be tracheotomized. In 1950, Creech and Ochsner reported five cases of tetanus in which tracheotomies were done.

Usually, in a small child it is better to perform the tracheotomy over a bronchoscope. In tetanus, however, to minimize any stimulus, the bronchoscope is not used. Preferably, tracheotomy is done through the second tracheal ring or lower to avoid subglottic stenosis. A long tracheotomy tube is preferable because a short tube sometimes rides outside the tracheotomy on flexing the head. A long tube can be shortened by wrapping some petrolatum gauze around the stem.

By-pass tubes have an opening on the under surfaces and allow air to go through the larynx. Frequently, secretions may plug and block off the opening and encroach on the luminal diameter of the tube. In my opinion, by-pass tubes should not be used early, and used possibly at the end-stage of decanalization.

Frequently, bleeding and crusting result following repeated suctioning of the tracheotomy tube. Catheters that have only one opening are frequently put into the tracheotomy with the suction pressure on. The negative pressure is allowed to build up. Immediately on reaching the end of the tube the mucosa is traumatized. Actual tearing of the mucosa with hemorrhagic edema, as seen on bronchoscopy in this particular case, can occur. Suctioning should be only as necessary, not by a time clock as is so often done.

A suction tube should be cut so that the tip is beveled, with multiple openings above. The multiple opening disperses the pressure. The suction tube should be inserted with the suction off and should slowly and progressively be withdrawn after the suction machine is turned on. This avoids building up a negative pressure and minimizes mucosal trauma.

DR. HARTMANN.—In this child the dose of Avertin was large enough to

produce muscle relaxation; it was also large enough to produce cessation of respiration. Thus, it was necessary to use a tank respirator. When the anesthetic was lightened, muscle spasm again became manifest, and even with the use of the respirator, ventilation was often ineffectual. Under these circumstances, the breathing bag was lifesaving. Since you were responsible, Dr. Eastwood, for introducing its use to us, will you comment on it?

DR. EASTWOOD.—Manual compression of the breathing bag attached to the tracheotomy tube increased ventilation by compensating inadequate pressure differentials obtained by the tank respirator. One problem encountered was that this bag was heavy, and when attached to the tracheotomy tube, the other end of the tube injured the mucosa of the trachea.

In an emergency, oxygen can be placed directly on the tracheotomy opening at 10 liters per minute for a fraction of a second and then released, but this is extremely dangerous, for if it is improperly done, rupture of the lung may result.

A respirator should fulfill the following requirements for optimal function: (1) 100 per cent humidity, (2) a temperature of 37° C., (3) reliability, (4) 10 to 30 cm. H_2O positive pressure to 5 to 15 cm. H_2O negative pressure, (5) the patient should be able to cycle it. At present, there is no respirator which fulfills the above.

DR. HARTMANN.—This patient never had a period of deep cyanosis, and there was no prolonged massive atelectasis. This brings up the question whether tetanus involves only motor nerves and whether this process is reversible. One previous patient with tetanus exhibited a picture which resembled clinically both rabies and bulbar poliomyelitis. Dr. Watkins, you found something in the literature concerning this, didn't you?

DR. T. K. WATKINS (Junior Resident).—In 1942 and 1943, Baker at the University of Minnesota reported twelve cases of tetanus in which there was involvement of the central nervous system. In two of the patients the dorsal nucleus of the tenth cranial nerve tended especially to be involved.

DR. HARTMANN.—Dr. Smith, would you comment on this work?

DR. DAVID SMITH (Assistant Professor of Pathology).—Baker called attention to neuronal changes, minimal perivascular demyelinization, and petechiae in the central nervous system of patients dead of tetanus. Although he reported two instances of lesions in the dorsal motor nucleus of the vagus, it is significant that he described several other cases in which he could find no such lesions. Present physiologic concepts of the brain stem, furthermore, do not assign an important role to this nucleus in respiration. It seems more likely that the anatomic lesions that have been described by Baker and others are more the effect of the respiratory arrest than its cause. Investigations by Harvey suggest that the major site of action of the tetanus toxin is peripheral and at the myoneural junction, although there may also be an excitatory effect on the central nervous system that is manifest by a reflex element in some spasms.

DR. HARTMANN.—This child's urinary output was diminished; edema and chemical changes of renal insufficiency developed. Anoxia and pneu-

monia may have been the cause of the renal failure. Dr. Moyer, will you tell us how acid-base imbalance occurs in such cases?

DR. MOYER.—You should be the one to do that.

DR. HARTMANN.—Her serum CO_2 content was approximately twice normal, but the pH was never elevated. Chloride was always lower than normal, but its degree of diminution was never as much as the HCO_3^- was increased. Therefore, she had a respiratory acidosis.

Acidosis is respiratory in origin due to accumulation of carbon dioxide or is metabolic in origin due to loss of $BHCO_3$. Normally, HCO_3^- plus Cl^- is equal to 125 meq. In a metabolic alkalosis, HCO_3^- plus Cl^- is equal to a figure less than 125 meq. In respiratory acidosis, HCO_3^- plus Cl^- is equal to a figure greater than 125 meq. In metabolic acidosis, HCO_3^- plus Cl^- is equal to a figure less than 125 meq., unless the acidosis is HCl in type.

When the body retains $BHCO_3$, the Cl will diminish, but more slowly than $BHCO_3$ increases. Thus, the sum of these two is greater than 125 meq. This patient's urine was acid, and as her respirations improved with recovery, her urine became alkaline because $BHCO_3$ was excreted and Cl retained.

When cellular metabolism takes place, acetate (C_2) reacts with (C_4) to produce carbon dioxide and water. Carbonic acid is thus formed. Such carbon dioxide is gotten out of the body in several ways. Some carbon dioxide combines with water, producing carbonic acid. However, there is about one thousand times as much carbon dioxide dissolved in water as there is carbonic acid.

$$C_2 + C_4 \rightarrow CO_2 + H_2O \rightleftharpoons H_2CO_3 \rightleftharpoons H^+ + HCO_3^-$$

Carbon-dioxide retention can be caused by pulmonary pathology, inadequate circulation due to cardiac disease, and by diminished respirations.

DR. JAMES MASON (Junior Resident Physician).—In 1924 and even before that, carbon dioxide was used experimentally as an anesthetic agent. When high blood concentrations of carbon dioxide are attained, a narcotic effect is noted. Other effects reported have been increased depth of respiration, increased blood pressure, myoclonic movements, flushing, increased cerebrospinal pressure, and even decreased coagulation time of the blood.

Carbon-dioxide narcosis can occur in severe pulmonary disease especially after the administration of oxygen. The respiratory center is no longer driven by anoxia, and there results reduced pulmonary ventilation. Carbon dioxide accumulates to even a greater degree, and carbon-dioxide narcosis ensues—a vicious cycle. When oxygen is administered to such a patient, the concentration should be very gradually increased to prevent this trouble.

DR. MOYER.—The HCO_3^- was approximately doubled, while the pH was normal. Therefore, the ratio of $BHCO_3 : H_2CO_3$ was still 20:1, and one can safely infer that the concentration of carbon-dioxide anhydride was approximately doubled and that the carbon-dioxide tension was likely about 80 mm. Hg. A level of 70 mm. carbon-dioxide tension will begin to depress respirations. The amount of depression will vary with the individual. Carbon-dioxide anesthesia might well

have played a part in the respiratory depression of this case. Hypertension and unconsciousness can also result from increased tension of carbon dioxide.

DR. HARTMANN.—Actually, carbon dioxide dilates the blood vessels and yet causes hypertension. This child's blood pressure varied but was usually high. This could possibly be explained by the tetanic convulsions which she had. One can postulate that the pressure of the cuff had to be increased in order to compress the brachial artery underlying muscles in tetanic contraction.

Dr. Moyer, you suggested placing this child in a flat position rather than the Trendelenburg position because you thought her diaphragm was weak and that the Trendelenburg position would result in inadequate respiration. We had her in this position in order that secretions might drain more easily.

DR. MOYER.—Gessel found among early experiments with dogs that respiratory exchange was diminished in the Trendelenburg position and that it improved when the animals were raised to the horizontal position. It has been shown that respiratory exchange can be diminished as much as 60 per cent during spinal anesthesia when the patient is in the Trendelenburg position and more especially in a fat person. The diaphragm is often not strong enough to maintain adequate breathing when one is in the Trendelenburg position.

DR. HARTMANN.—Is there a central nervous system lesion in tetanus?

DR. O'LEARY.—I do not believe there are primary lesions of the central nervous system in tetanus. If tetanus has a central effect, it is likely to be an excitatory one, such as the state effected experimentally in strychninization. The pons, medulla, and reticular internuncials of the fifth nucleus control the jaw muscles. Hoff of Baylor claims that the medulla contains an apneustic center and that the pontine respiratory center plays into the lower apneustic one. Considering the possibilities for primary excitation of the pontine center, its effect on the medullary center may well be superior. However, I believe the primary action of tetanus toxin to be at the myoneural junction.

DR. JEAN V. COOKE.—It has become apparent that prophylactic doses of 1,500 units of tetanus antitoxin giving a passive immunity for only two to three weeks are often inadequate. If a real hazard of tetanus exists, larger doses of 5,000 to 10,000 units should be given with a considerably longer period of passive immunity. Therapeutic doses should be 60,000 to 100,000 units which will neutralize any free toxin formed subsequent to the injection for a period of six to ten weeks. Toxin absorbed previous to the giving of antitoxin and combined with body cells cannot be neutralized. Repeated doses of antitoxin are quite unnecessary if an adequate dose is given initially.

The presence of more than small amounts of passive antitoxin in the body apparently inhibits the production of an active antitoxic immunity by tetanus toxoid. In a patient with tetanus after an adequate large therapeutic dose of antitoxin, toxoid injections started four weeks later and continued every two weeks for a total of

four doses will induce a persistent active immunity. The fact that it is thus possible to maintain a continuous immunity in the patient—first passive converted to an active immunity—eliminates the necessity for any attempt at excision of a possible wound focus of infection.

Since 1933, when we instituted the current type of therapy with Avertin sedation, we have treated forty-seven patients in this hospital with ten deaths, a total mortality of 21.3 per cent.

DR. HARTMANN.—In summary, our treatment consists of sedation with rectal Avertin in a dose of 80 mg. per kilogram as the initial dose with almost always an additional dose of 20, 30, or 40 mg. per kilogram in an hour or two to get the proper degree of sedation. Following the first sedation, 50,000 units of tetanus antitoxin intravenously and 50,000 units intramuscularly should be given. A tracheotomy should be performed on most patients to insure an adequate airway. Special nurses for twenty-four-hour duty are required. Antibiotics should be used prophylactically or therapeutically in the presence of infection such as a complicating pneumonia. It is necessary to support these children by artificial methods of fluid and food administration. The parenteral route of administration is preferred. In addition to glucose and lactate-Ringer's, one can add Amigen, albumin, and blood where there is a real problem of maintaining nutrition. Probably an older child can be tube-fed if a nurse is in constant attendance to suck out the trachea in case of aspiration, but I would hesitate to use tube feedings in a young child.

Comments on Current Literature

SMALLPOX VACCINATION AND PREGNANCY

THE opinion that vaccination for smallpox during pregnancy exerts no harmful effect upon the fetus has been held by physicians in general. In an article appearing in *Lancet* (Dec. 6, 1952), Patrick MacArthur[1] questions this general conclusion and presents epidemiologic studies which tend to support his contention.

A particular instance led MacArthur to investigate this problem. As the result of an outbreak of smallpox in the West of Scotland in 1950 a large number of persons was vaccinated. Among them, one young woman came to his attention who was approximately three months pregnant at the time of vaccination. She had not been vaccinated previously, and experienced a severe primary reaction. Three months later this patient delivered spontaneously "a feeble hydropic premature infant covered with a very severe generalized vaccinia." The child died eighteen hours after birth. Clinical and pathologic studies carried out by Macdonald and MacArthur[2] established to their satisfaction the diagnosis of fetal vaccinia. MacArthur refers to another case of fetal infection with vaccinia, that recorded by Lynch in 1932.[3] In this instance vaccination was carried out during the fifth month of pregnancy and spontaneous delivery occurred at the sixth month. The feeble hydropic infant was covered with pustular lesions, and died within a few hours. The amniotic fluid was described as excessive in amount, rather viscid in consistency, and the placenta as "studded with white flecks." Lynch refers to other cases of fetal vaccinia recorded in the literature. In this rather extensive review of dermatologic conditions of the fetus, Lynch presents forty-seven cases of variola in the pregnant woman in which the child showed a pustular eruption, or healed scars, at spontaneous premature delivery, or at birth. In pregnant animals experimental intrauterine infection with the virus of vaccinia has shown similar fetal manifestations.[4]

With these facts in mind, MacArthur undertook a careful follow-up study of the large number of persons being vaccinated in West Scotland during the outbreak of smallpox in 1950. He chose the prospective type of inquiry, following the patients who were pregnant at the time of vaccination during the remaining pregnant period, rather than the retrospective method of accumulating data and then determining the results in retrospect.

Accordingly, each woman under 45 years of age whose registration blank carried the title, Mrs., received an additional questionnaire requesting the name of the attending physician, and the proposed place, and the date of confinement, if the woman was pregnant, and requesting return of the blank stating whether or not she became pregnant within the three-week period following vaccination. A total of 3,408 of the questionnaires was received. Of this number there were 203 women who developed a definite "take," who were pregnant at the time of vaccination, or who became pregnant within the two- to three-week period following the day of vaccination. Of these, sixty-seven were in the first trimester of pregnancy, sixty-nine in the second, and sixty-seven in the third trimester. The accompanying table is an analysis of the information gained from these questionnaires.

It is significant that thirty-four women who had successful vaccinations during the fourth through the twelfth weeks of pregnancy yielded 47 per cent abnormal products of pregnancy.

MacArthur attempts to compare these striking figures with collected data expressing the fetal loss in a comparable group of pregnant women in the absence of vaccination procedure, and concludes that the highest possible mortality in a control group would be of the order of 13 per cent fetal loss. In his series of patients vaccinated during the first trimester, including women who became pregnant within two weeks following vaccination, fetal loss was 24 per cent.

On the basis of this study, MacArthur concludes that "vaccination of a pregnant woman during the first trimester of pregnancy, and especially during the second and third months of pregnancy, significantly increases the fetal mortality." The author emphasizes that miscarriage or stillbirth represented most of the fetal loss, and at this time he is not willing to make any statement concerning the possible role of vaccination for smallpox as a cause of congenital abnormalities in children.

Whether congenital vaccinia might prove to be a common finding is open to some question. However, in the light of this interesting investigation it would seem advisable that, if at all possible, vaccination of the pregnant woman be avoided during the first trimester of pregnancy. On the other hand, it seems reasonably clear that vaccination for smallpox during the second and third trimesters of pregnancy has little or no effect on the outcome.

Since in present times, outbreaks of smallpox are being recorded in significant numbers, and since a given population may not be maintaining immunity to this disease,[5] the problem of vaccination or revaccination of adults will present itself to the physician. If, because of actual contact with smallpox, it becomes necessary to vaccinate a pregnant woman in the first trimester of pregnancy, the family physician and the health officer should be aware of the danger of vaccination during pregnancy. Such patients should be followed carefully, and also a careful record kept of the results of the procedure. Knowledge concerning this important subject is needed. Careful post-mortem studies of abortion and stillbirth material might yield information concerning the pathologic changes in the fetus which result in death. Such investigations should include appropriate virus studies including determination of antibody titer in the blood of the mother, and, if possible, in that of the offspring.

Detailed records as to the incidence of vaccination for smallpox in pregnant women, and careful follow-up study of the infants resulting, might throw light on the possible role of vac-

TABLE I. ANALYSIS OF REPLIES TO QUESTIONNAIRE

STAGE OF PREGNANCY	NO. OF WOMEN	RESULT OF PREGNANCY	PERCENTAGE OF ABNORMALS
Less than 4 weeks +	32	Normals	3
Women who became pregnant within 2 wks. after vaccination	33	1 Miscarriage	24
4-12 wk.	34	17 Normals	47
		1 Normal premature	
		10 Miscarriages	
		5 Stillborn	
		1 Congen. abnormality	
2nd trimester	69	66 Normals	3
		1 Normal premature	
		1 Stillborn	
		1 Neonatal death	
3rd trimester	67	63 Normals	2
		3 Normal prematures	
		1 Cerebral birth trauma	

cinia as a cause of congenital malformations.

RUSSELL J. BLATTNER.

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News and Notes

Dr. Edwin E. Graham of Philadelphia died June 11, 1953, aged 89. After receiving an A.B. degree from Harvard, he studied medicine at Jefferson Medical College, receiving his M.D. degree in 1887. Following foreign study in Germany, he began the practice of pediatrics in Philadelphia. In 1904 he was appointed to the first professorship of pediatrics established at Jefferson, which he held until 1938 when he became Emeritus Professor. In 1950 he was given the honorary degree of Doctor of Science by Jefferson. He was elected to the American Pediatric Society in 1897 and was president of the society in 1919. He was the author of a textbook for students, *Children's Diseases*. For several years he was a member of the Editorial Board of the *American Journal of Diseases of Children*. In 1907 he was chairman of the Section on Pediatrics of the A.M.A.

Dr. Alan Ross has been appointed Professor of Paediatrics, McGill University, and Physician-in-Chief, The Children's Memorial Hospital, as of July 1, 1953.

Dr. Alton Goldbloom has been named Professor Emeritus of Paediatrics at McGill University, and Consulting Physician at The Children's Memorial Hospital.

A postgraduate course in **Pediatric Allergy** under the direction of Dr. Bret Ratner will be given next winter at the **New York Medical College**. There will be thirty sessions on Wednesdays, beginning Nov. 4, 1953, and continuing through May 31, 1954. Applicants must have been certified in pediatrics or meet the requirements for certification. Detailed information may be obtained from the Dean of the college, 106th St. and Fifth Ave., New York 29.

Under the auspices of the Minnesota Heart Association, the **University of Minnesota** will present a Symposium on Cardiovascular Physiology and Surgery Sept. 14 to 16, 1953, in the Museum of Natural History Auditorium on the University Campus. A host of internationally known physiologists and vascular surgeons will participate. The symposium will be open, without tuition fee, to all physicians and to qualified investigators in the field of cardiac physiology. Housing accommodations will be available on the campus for out-of-town registrants who wish them. Further information may be obtained from the Director, Department of Continuation Medical Education, University of Minnesota Hospitals, Minneapolis 14, Minn.

The **Second International Congress** of **Cardiology** will be held in Washington, D. C., Sept. 12 to 15, 1954. It will be immediately followed by the Annual Scientific Sessions of the American Heart Association, Sept. 16 to 18, 1954. The opening session will be held in the auditorium of Constitution Hall at 10:30 A.M. on Sunday, September 12, with addresses of welcome. The Scientific Sessions lasting for three days will include formal papers, panel discussions, clinical pathological conferences and visits to important medical centers in Washington and Bethesda. The program will be printed in French, Spanish, and English. Immediate translation of some of the papers and discussions will be made in three languages. A series of Post-Congressional visits and conferences to at least twenty of the leading cardiac clinics in different parts of the United States and Canada has been arranged by special committees of local heart associations in the various cities. Further information may be obtained from Dr. L. W. Gorham, Secretary-General, 44 East 23rd St., New York 10, N. Y.

The Biennial Conference of the **National Association for Nursery Education** will be held in Minneapolis from Oct. 28 to 31, 1953. The program will include sections on: Administration of the Nursery School; Parents; Research; Legislation and Standards for Nursery Schools; Television; Cooperative Nursery Schools; Nursery Schools for Exceptional Children; Nursery School in Relation to Later School Experiences. Among the speakers will be Dr. James L. Hymes, Jr., and "Miss Frances" of Ding Dong School. Programs and registration blanks may be obtained from the Conference Chairman, Dr. Elizabeth Fuller, Institute for Child Welfare, University of Minnesota, Minneapolis. The headquarters hotel is the Hotel Nicolette and reservations should be made directly with the hotel.

Book Reviews

Kinderärztliche Notfallfibel. Prof. Dr. B. de Rudder, Stuttgart, 1953, Georg Thieme Verlag, 185 pages. Price 13.50 D.M.

This is an enlarged and revised edition of the text on pediatric medical emergencies by the Director of the University Children's Clinic at Frankfurt. The text is quite complete, but so many conditions are included that the discussion of each is rather sketchy. For example, pages 8 to 40 discuss respiratory and breathing difficulties and some fifteen causes are included. Under the heading "acute prostration (including collapse, coma, toxicoses)," some seventeen topics as anaphylactic shock, diabetic coma, hypoglycemia, meningitis, sepsis, etc., are discussed. Some of these as "toxic scarlet" are practically never seen in the United States. Other general headings are convulsions, hemorrhage, persistent vomiting, icterus, acute abdominal pain (ileus, pneumococcic peritonitis, and acute appendicitis are the three discussed), and acute poisonings. A short section is given to technical methods of treatment such as baths, packs, intubation, and the "iron lung." The discussion of the techniques of the "iron lung" is only a page and a half in length. The author has attempted to cover too much in this volume of less than 200 pages, with the result the text is more of an outline than a discussion of pediatric emergencies that threaten life.

Nervous System. Frank H. Netter, M.D., Summit, N. J., 1953, Ciba Pharmaceutical Products, 143 pages, 104 color plates. Price $6.00.

Thanks is due to the Ciba Company for making available in atlas form the beautiful color plates of the nervous system by Dr. Netter. In all there are 104 large color plates with descriptive text. Seventy-two of these deal with the anatomy of the spine, central and autonomic nervous systems, and functional neuroanatomy. Thirty-two are descriptions of pathologic lesions of the brain and cord. Dr. Netter's skill and work are too well known and admired to need comment. The plates are of exceedingly high quality. There is a brief foreward by Dr. John F. Fulton.

The Conception of Disease. Walther Riese, M.D., New York, 1953, Philosophical Library, 120 pages. Price $3.75.

In this unusual book Dr. Riese, formerly on the staff of German and French universities and now a member of the staff of several Virginia schools and organizations, discusses the various conceptions of disease as they have developed in succeeding periods of civilization: platonic, anthropological, moral, physiologic, anatomical, etiological, social psychologic, ontologic, and metaphysical.

Rehabilitation of the Physically Handicapped. Henry H. Kessler, M.D., New York, 1953, Columbia University Press, 275 pages. Price $4.00.

This is a revised version of the book on the handicapped written in 1947 by Dr. Kessler, medical director of the Kessler Institute for Rehabilitation at West Orange, N. J., who has been one of the leaders in the field of rehabilitation. It is a general discussion of rehabilitation rather than a technical manual, and the approach is broad. After a discussion of the physically handicapped, including the crippled child, the injured worker, the disabled veteran, and the chronic disabled, the author takes up the general principles upon which rehabilitation is based, as rehabilitation centers which have been rapidly increasing, vocational guidance, training, and placement.

A third section discusses rehabilitation in practice, with chapters on the mentally and emotionally disabled, the orthopedic patient, the blind and deaf, and medical and surgical invalids. In a final section the need of a national program is presented.

It is a most thoughtful and interesting discussion by a leader in the field who is familiar with all the phases involved in the rehabilitation of the physically handicapped. It is a subject that has many facets, medical and orthopedic care, insurance compensation, legislation, and education. The reader will find this book a well-written, excellent background presentation of a field which is rapidly developing and expanding.

Editor's Column

THE FRIVOLOUS USE OF ANTIBIOTICS

THE profound changes wrought by the introduction of sulfonamides and antibiotics in the treatment of infectious disease have led to much philosophizing regarding the over-all results of such therapy. Experience has substantiated to varying degrees predictions that patients might be sensitized to these agents, that there might be interference with normal immune mechanisms, that resistant strains of organisms might emerge, that unusual pathogenic effects might be encountered due to organisms not suppressed by these agents, and finally that deleterious effects might be caused by the agents themselves.

It was announced during the past year that blood dyscrasias had resulted from the use of chloramphenicol. That this news should occasion surprise and consternation is unrealistic and almost naïve. If one were to list the agents, ancient and modern, in which therapeutic usefulness is accompanied by occasional serious or fatal side effects, it would include almost every drug of real value: mercurials, iodides, arsenicals, quinine, serums, sulfonamides, antibiotics, ad infinitum.

Almost unfailingly, new drugs have been introduced with the promise of great potency and of complete innocuousness only to have their limitations and occasional harmfulness demonstrated by experience. It is entirely possible that our experience with many of these agents remains incomplete.

The phrase "broad spectrum antibiotics" has led to the uncritical use of these substances without reference to specific etiology, to the employment of combinations or successions of therapeutic agents in dizzying array, and to their use in such infections as influenza, mumps, measles, and other virus diseases with no concern over the fact that in not one of these is there any demonstrable value. The use of antibiotics in the prevention of complications of otherwise insusceptible infections presupposes that these complications will be due to pneumococci, beta streptococci, or other susceptible organisms, and bids fair to increase the complications due to pseudomonas, klebsiellae, moniliae, and other refractory microbial causes. Furthermore, the capricious use of antibiotics frequently results in inadequate dosage in those moderately resistant infections which might respond to intensive therapy.

All these considerations are of especial concern in the treatment of childhood infections. The adult, by and large, is infrequently ill and may not be repeatedly exposed to antibiotic therapy. The average child, on the other hand, may have some infectious disease several times a year throughout his period of growth. If on the occasion of each illness the child is given one or another antibiotic and has surgical or traumatic experiences thus "covered," the end result may be dismaying and bear out all of the fears which are based upon logic and experience.

It is impossible to defend the frivolous, uncritical, and indiscriminate use of therapeutic agents of extreme potency. There is good reason to expect occasional unfortunate effects, and therapeutic risks can be justified only by the severity of infection and the establishment of the etiology within reasonable bounds. No one can object to the use of a specific agent in the treatment of a severe infection of known etiology. It is often justifiable to treat disease on the basis of the clinical estimate of probable etiology. There is little to recommend the indiscriminate medication of infections of varying severity and undetermined etiology in this manner. The hunter who lets go both barrels in the direction of a flight of ducks, no matter how numerous the birds, bags but few. The best shooting results from the choice of an appropriate charge and deadly aim at a selected target.

E. B. S.

FOUNDER MEMBERS OF THE AMERICAN PEDIATRIC SOCIETY

DR. John Dorning of New York, who died in April, was the last surviving member of the group of forty-two who founded the American Pediatric Society in 1888. A look at the membership roster of sixty-five years ago impresses one with the leadership given by this group to pediatrics in its early years and their many contributions to American medicine: Jacobi, Holt, Koplik, and O'Dwyer of New York, William Pepper and Keating of Philadelphia, Rotch of Boston, Victor Vaughan of Ann Arbor, Blackader of Montreal, Forchheimer of Cincinnati serve as examples.

Another striking thing was the longevity of this group. Dorning lived 93 years and Jacobi was 89 at the time of his death. Among those who died in their eighties were Blackader, Carr, Chopin, Huber, and Northrup. Vaughan reached 78, John Reid 77, and Louis Starr 76 years. Quite a few others reached "three score and ten" or more, and a number, as Holt and Koplik, missed this span by only a year or so. Life expectancy for males born in 1840 to 1860 was not near these figures, and it is interesting to speculate on the reason for the longevity of this small group. While many were teachers, the well-recognized longevity of college professors living in a "protected environment" is not applicable, as all were active practitioners. Perhaps there is some subtle relationship between pediatrics and geriatrics due to work with children keeping one young in years as well as in spirit. More probably it was a rugged group to begin with, who had the constitution to live through the years of high mortality in early life which made life expectancy a hundred years ago much less than it is today.

THE CARE AND COST OF A CASE OF TETANUS

ASIDE from its technical interest the Clinical Conference on page 220 of this issue strikingly reflects some of the changes which have taken place in the practice of medicine in our children's hospitals and medical centers in recent years, and the techniques now in use as a result of the remarkable advances in medical science. The 11-year-old ward patient was in the hospital fifty-one days. Most of the time she was critically ill and at times in a moribund condition. In addition to around-the-clock care by the resident staff under the direction of the pediatric chiefs of service, the heads of the departments of surgery, otolaryngology, anesthesiology, and neurology in the medical center were in constant consultation in the treatment and contributed to her recovery. It is not an unusual or unique picture, as comparable types of medical care and treatment are being given daily in many hospitals throughout the country.

It is also of interest when considered from the cost standpoint. The hospital cost was $2,100 of which $382.50 represents the ward rate and the balance special nursing, oxygen, helium, transfusions, and medicines. It is impossible to calculate the monetary value of the medical skills involved, but we are sure it would have been overwhelming on a fee-for-service basis. Modern techniques are in part responsible for the increased cost of hospital care from $5.00 to $7.00 only a few years ago to around $15.00 per day. On the credit side they have saved lives, shortened the average period of hospitalization, and prevented chronic illness and permanent disability.

In contrast to the treatment reflecting the advances of medical science, the case also strikingly reflects the failure to use modern medical science. Had the child been immunized with tetanus toxoid, as all children should be as a matter of routine, and a booster dose given at the time of the barnyard accident, not only would an almost fatal illness have been prevented, but the cost to the parents and the community would have been avoided.